Palliative Care in Patients with Noncancer Illness

by

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A thesis submitted in conformity with the requirements
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Institute of Health Policy, Management & Evaluation
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Abstract

The evidence base for palliative care is heavily skewed toward patients with cancer, despite the fact that there are twice as many patients with palliative care needs and noncancer illness. This thesis seeks to establish the evidence for clinical practice and policy development for palliative care programs to improve end-of-life care. The first study was a systematic review and meta-analysis of randomized clinical trials of patients with primarily noncancer illness. We found that receipt of palliative care, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, and no significant difference in quality of life. The second study measured the association between newly initiated palliative care in the last 6 months of life, healthcare use and location of death in a cohort of adults dying from noncancer illness; and compared these associations with those who die from cancer. We found that among those dying of chronic organ failure, palliative care was associated with a reduction in the rate of emergency department use, hospitalizations and ICU admissions. Palliative care was associated with increased rates of emergency department use and hospitalization in patients dying of dementia, which differed depending upon whether they lived in the community or in a nursing home. In our third

study, we measured the association between physician rates of referral to palliative care and location of death in hospitalized adults with serious illness, which include patients dying of cancer and noncancer illness. We found that patients who were cared for by physicians with higher rates of referral to palliative care were less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation in referral as a barrier to access. Collectively, these thesis findings highlight the potential benefits of palliative care in patients with select noncancer illness and identify further knowledge gaps for other common noncancer illnesses. Scaling existing palliative care to increase access through sustained investment in physician training and current models of collaborative palliative care may improve end-of-life care, which have significant implications for health policy.

Acknowledgments

My inspiration for this work comes from the thousands of patients I've cared for with serious illness. They serve as a constant reminder that our healthcare system isn't perfect and they continue to fuel my passion to improve it through research and advocacy. I am grateful to have had the privilege to learn from my experiences with them.

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grants, to publish meaningful work with a razor-sharp focus on policy, and to be a strategic leader. Most of all, I've learned how to look after my family and plan for the future; that, and how to quote Rush songs in my academic work.

Above all, I am so fortunate to have the unwavering love and support of my parents and in-laws, my brothers (plus Robbie), wife Lynn, and incredible children Hunter, Austin and Kennedy. You are what makes this all worthwhile.

Table of Contents

Published Thesis Work

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List of Tables

List of Figures

Chapter 1 - Introduction

Chapter 2 - Study #1 – Association of Receipt of Palliative Care Interventions with Healthcare Use, Quality of Life, and Symptom Burden Among Adults with Chronic Noncancer Illness: A Systematic Review and Meta-analysis

1 Introduction

1.2 Thesis Background

1.2.1 The challenges of end-of-life care for patients with chronic terminal illness

Every year, 280,000 Canadians die.[1] Populations are aging, in part due to the increases in life expectancy afforded by advances in medicine.[2] Consequently, the prevalence of common chronic terminal diseases such as cancer, heart failure (HF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), cirrhosis, dementia and stroke are increasing.[3–7] These chronic diseases are associated with significant functional disability, high symptom burden and a reduced quality of life, especially near the end of life.[3,8–11]

End-of-life care is also associated with high health expenditure. Approximately 10-13% of annual health costs are devoted to the care of patients in their last year of life.[11–13] Half of these incurred end of life costs were accrued in the acute care setting,[11,14,15] as nearly 75% of individuals are hospitalized and more than half of patients are admitted to intensive care units (ICU) near the end of life.[16] Some elements of end-of-life care delivered in the acute care setting may be of limited benefit, and are also associated with poor quality of life (QOL).[8–10,17–19] Therefore, the delivery of care in the hospital setting, along with invasive clinical interventions such as admission to the ICU, mechanical ventilation and major surgery at the very end of life may therefore be viewed as of low- or uncertain-value for many patients.[20–22]

Importantly, current trends in the delivery of end-of-life care often do not align with the type of care individuals want as they approach death. Seventy percent of Canadians report that they would prefer to focus on quality, not quantity of life in these

circumstances.[23] A recent review of twenty studies as part of this thesis work examining patient and societal views on priorities for care at the end of life found 75% reported that participants prioritized improvements in QOL over life extension at the end of life.[24–43] Further, most patients prefer to die at home.[23,44–51] A home death and avoidance of unwanted healthcare use are considered quality indicators for end-of-life care.[44–49,52–55] Unfortunately, up to 60% of patients continue to die in a hospital.[46,48,56] In the era of patient-centred medicine, health systems continue to struggle to deliver the type of care that individual patients want.

1.2.2 An aim to deliver high-value care

Health systems and decision makers are increasingly focused on the delivery of high-value care at the end of life to reduce suffering and improve quality for the lowest possible cost. This renewed attention is propelled by the aging and increasingly medically complex population with a high burden of suffering and health expenditure.

High-value care is variably defined in the literature as the quality of health care achieved per unit of cost.[57–61] The Institute of Medicine defines high-value care as "the best care for the patient, with the optimal result for the circumstances, delivered at the right price."[61] However, variation in the definition of high-value care can arise from differences in focus on various components of the value equation.[62] A more patient and caregiver focused lens that emphasizes safety, experience, and affordability may define high-value care in the context of its ability to achieve the patient's expressed goals with little attention to the associated costs.[59,63] In contrast, traditional health economic frameworks emphasize the evaluation of value using cost-effectiveness, which

measures the balance between achieving improved health outcomes and dollars spent.[57]

1.2.3 Challenges in achieving value in healthcare at EOL

The challenge of achieving high-value care is a vexing problem facing healthcare systems. In some cases, excess waste in healthcare related to failure of care delivery, failure of care coordination, overtreatment, and administrative complexity contributed to difficulty in improving value across the healthcare system.[20,21] In other cases, policy interventions were too diffuse, failing to focus on the most important issues for any specific group of patients, such as those at end of life. Many of these policies have targeted specific diseases or individual elements of care (e.g., hospital readmission in heart failure) and have overlooked what patients indicate is most important to them.[64]

Some have suggested that improving value of care may be achieved by focussing on specific subgroups of patients such as those at end of life.[64] This group of patients have some of the highest associated health expenditure, have high health care needs, and are at high risk of having those needs unmet.[45,46,65–68]

1.2.4 The promise of palliative care

The term *palliative care* was created in 1975 by Balfour Mount, the founding Director of the Royal Victoria Hospital Palliative Care Service in Montreal, Quebec. The word palliative means literally “to improve the quality of”. Palliative care focuses on improving QOL, reducing suffering, and helping with decision-making for patients with serious illness and their caregivers.[68,69]

1.2.5 Benefits of palliative care for patients and caregivers

The collective evidence for the benefits of palliative care come from five recent systematic reviews and meta-analyses of patients with serious illness, including one from this thesis work. Overall, palliative care improves quality of life, patient and caregiver satisfaction, advanced care planning, and reduces symptom burden and healthcare use.[68–72]

A 2016 systematic review and meta-analysis included 43 RCTs of palliative care interventions compared to usual care in 12,731 patients with serious illness (70% in patients with cancer).[69] A similar 2017 systematic review and meta-analysis included 12 studies (10 RCTs) of specialized palliative care interventions compared to usual care (defined as using a interprofessional team approach) in 2,454 patients with serious illness (72% in patients with cancer).[70] Both studies demonstrated that palliative care was associated with significant improvements in QOL and symptom burden. In the 2016 review, there was no association between palliative care and survival. However, palliative care was consistently associated with improvements in advance care planning, patient and caregiver satisfaction, and lower healthcare use and costs.

A separate 2016 systematic review examined 124 RCTs in patients with serious illness (67% in patients with cancer; total number of patients not reported) for the elements of palliative care delivery (personnel, use of interprofessional teams, setting of care) that were effective in achieving better outcomes for patients, caregivers, and the healthcare system. That study demonstrated that the benefits of palliative care, such as improved QOL or reduced symptom burden were most pronounced with the involvement of nurses and social workers and the use of an interprofessional team.

Home-based palliative care also associated with improved patient and caregiver outcomes. Palliative care also improved communication and advance care planning.[71]

A third systematic review of 15 studies (8 RCTs) published in 2016 examined palliative care interventions in patients with HF. The majority of studies included in the review demonstrated improvements in quality of life and satisfaction with care. The authors performed a meta-analysis in 3 RCTs and found that home-based palliative care was associated with a 42% lower risk of rehospitalization.[72]

Finally, our systematic review and meta-analysis of 28 RCTs of palliative care interventions in 13,664 patients with noncancer illness (36% in patients with HF) demonstrated associated reductions in acute healthcare use and symptom burden, and increases in advance care planning, compared to usual care. There was no association with QOL. The benefits of palliative care were found to be associated with the presence of a specialized palliative care physician and an interprofessional care team.[68]

However, the collective evidence for palliative care continues to be heavily skewed toward patients with cancer and heart failure. The evidence for other common terminal conditions such as COPD, ESRD, cirrhosis, dementia, stroke, HIV/AIDS, and neurodegenerative conditions such as amyotrophic lateral sclerosis and multiple sclerosis are limited.

Given its patient-centred focus, palliative care may be able to achieve high-value care by helping to achieve a patient's specific goals regardless of its associated costs.[59,63]

1.2.6 Costs and Cost-effectiveness of palliative care

Recent work has begun to focus on the cost-effectiveness of palliative care and its association with healthcare costs.

A 2018 systematic review and meta-analysis examined studies of economic evaluations of palliative care versus usual care for hospitalized adults with serious illness (cancer; HF, COPD, ESRD, cirrhosis, AIDS/HIV; or selected neurodegenerative conditions). Six cohort studies comprising 133,118 patients were included in the analysis. Irrespective of diagnosis, associated hospital costs were significantly lower (US $3,237) in patients receiving palliative care. Patients with cancer had the highest associated reduction in costs (US $4,251) compared to patients with noncancer illness (US $2,105).[73]

A 2013 Cochrane review of 6 studies (5 RCTs) including 2,047 patients with advanced cancer, HF, COPD, HIV/AIDS and multiple sclerosis and 1,678 caregivers compared the resource use and costs associated with home-based palliative care compared to usual care. All studies measured institutional and non-institutional costs. All six studies reported lower costs in the palliative care groups with differences ranging from 18% to 35%. The study was unable to pool the cost differences across studies and the evidence was inconclusive with respect to cost-effectiveness of home-based palliative care compared to usual care.[50]

An earlier literature review in 2014 examined the evidence on the costs and cost-effectiveness of palliative care interventions across all healthcare settings. A total of 46 studies were included (5 randomised controlled trials (RCT), 2 non-RCTs, 34 cohort studies, 2 case studies, 2 before-and-after studies and 1 ‘other’ study). The findings were mixed and heterogeneous across care settings. Two RCTs found a significant

association with lower costs, whereas in 3 RCTs, no association was reported between palliative care and costs. The review included only 1 study that met criteria for measuring cost-effectiveness and found inconclusive results.[74]

Finally, in 2014 the Ontario Health Technology Advisory Committee completed an economic analysis of end-of-life interventions for Ontario patients in the last year of life. That study reported home-based palliative care was cost-effective because it increased the chance of dying at home by 10%, increased the average number of days at home by 6 days, increased gains in quality-adjusted life days by 0.5 and reduced costs (CAD $4,400) per patient. The results for the other interventions were uncertain.[75]

1.3 Thesis Structure

1.3.1 Study #1 – Association of Receipt of Palliative Care Interventions with Healthcare Use, Quality of Life, and Symptom Burden Among Adults with Chronic Noncancer Illness: A Systematic Review and Meta-analysis

Importance: The evidence for palliative care exists predominantly for patients with cancer. The effect of palliative care on important end-of-life outcomes in patients with noncancer illness is unclear.

Objective: To measure the association between palliative care and acute healthcare use, quality of life (QOL) and symptom burden in adults with chronic noncancer illnesses.

Data Sources: MEDLINE, EMBASE, CINAHL, PsychINFO and PubMed from inception to April 18, 2020.

Study Selection: Randomized clinical trials of palliative care interventions in adults with chronic noncancer illness. Studies involving ≥50% of patients with cancer were excluded.

Data Extraction and Synthesis: Two reviewers independently screened, selected and extracted data from studies. Narrative synthesis was conducted for all trials. All outcomes were analyzed using random-effects meta-analysis.

Main Outcome and Measures: Acute healthcare use (hospitalizations and emergency department use), disease-generic and disease-specific quality of life (QOL) and symptoms, with estimates of QOL translated to units of the Functional Assessment of Chronic Illness Therapy scale (FACIT-Pal, range, 0-184 [worst-best]; minimal clinically important difference [MCID], 9 points) and symptoms translated to units of the

Edmonton Symptom Assessment Scale global distress score (ESAS, range, 0-90 [best-worst]; MCID, 5.7 points).

Results: Twenty-eight trials provided data on 13,664 patients (mean age 74 years, 46% female) (heart failure, 10 trials, n=4,068 patients; mixed disease, 11 trials, n=8,119 patients; dementia, 4 trials, n=1,036 patients; chronic obstructive pulmonary disease, 3 trials n=441 patients). Palliative care, compared with usual care, was significantly associated with lower ED use (9 trials, n=2,712, 20% versus 24%; odds ratio (OR) 0.82; 95% CI 0.68,1.00, I^2 = 3%), hospitalization (14 trials, n=3,706, 38% versus 42%; OR 0.80; 95% CI 0.65,0.99, I^2 = 41%) and modestly lower symptoms (11 trials, n=2,598, standardized mean difference (SMD) -0.17; 95% CI -0.27,-0.06, I^2 = 0%; ESAS mean difference -2.2; 95% CI -3.6, -0.8). Palliative care was not significantly associated with disease-generic QOL (6 trials, n=1,334, SMD 0.18; 95% CI -0.24,0.61, I^2 = 87%; FACIT-Pal mean difference 4.7; 95% CI -6.3,15.9), or disease-specific measures of QOL (11 trials, n=2,204, SMD 0.07; 95% CI -0.09,0.23, I^2 = 68%).

Conclusions and Relevance: In this systematic review and meta-analysis of randomized clinical trials of patients with primarily noncancer illness, palliative care, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, but there was no significant difference in quality of life. Analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit generalizability to other chronic illnesses.

1.3.2 Study #2 – Association Between Palliative Care and Healthcare Outcomes Among Adults Dying from Noncancer Illness: A Population-Based Matched Cohort Study

Importance: Palliative care is associated with reduced healthcare use and increased likelihood of death at home in people with cancer. Evidence for its association in people with terminal noncancer illness is limited and conflicting.

Objective: To measure the association between newly initiated palliative care in the last 6 months of life, healthcare use and location of death in adults dying from noncancer illness; and to compare these associations with those who die from cancer at a population level.

Design: Population-based matched cohort study using linked health administrative data.

Setting: Ontario, Canada between 2010 and 2015.

Participants: 113,540 adults who died of cancer and noncancer illness. Patients were directly matched on cause of death, hospital frailty risk score, the presence of metastatic cancer, residential location (according to 1 of 14 local health integration networks that organize all healthcare services in Ontario), and a propensity-score to receive palliative care that was derived using age and sex.

Exposure: Newly initiated physician-delivered palliative care in the last 6 months of life, administered across all healthcare settings.

Main Outcome Measures: Rates of emergency department visits, hospitalizations, admissions to the intensive care unit (ICU), and odds of death at home versus hospital following first consultation with palliative care, adjusted for patient characteristics.

Results: In patients dying from noncancer illness related to chronic organ failure – similar to cancer – palliative care was associated with statistically significant reduced rates of emergency department visits (crude rate [SD] 1.9 [6.2] versus 2.9 [8.7] per

person-year; rate ratio (RR) 0.88 [95% CI 0.85 to 0.91]), hospitalization (crude rate [SD] 6.1 [10.2] versus 8.7 [12.6] per person-year; RR 0.88 [95% CI 0.86 to 0.91]), ICU admission (crude rate [SD] 1.4 [5.9] versus 2.9 [8.7] per person-year; RR 0.59 [95% CI 0.56 to 0.62]) and increased odds of death at home (n=6,936 (49.5%) versus n=9,526 (39.6%); odds ratio 1.67 [95% CI 1.60 to 1.74]). In patients dying of dementia, palliative care was associated with increased rates of emergency department visits (crude rate [SD] 1.2 [4.9] versus 1.3 [5.5] per person-year; RR 1.06 [95% CI 1.01 to 1.12]), hospitalization (crude rate [SD] 3.6 [8.2] versus 2.8 [7.8] per person-year; RR 1.33 [95% CI 1.27 to 1.39]) and reduced odds of dying at home or in a nursing home (n=6,667 (72.1%) versus n=13,384 (83.5%); OR 0.68 [95% CI 0.64 to 0.73]), which differed depending upon whether they lived in the community or in a nursing home.

Conclusions: These findings highlight the potential benefits of palliative care in select noncancer illness. Scaling existing palliative care to increase access through sustained investment in physician training and current models of collaborative palliative care may improve end-of-life care, which may have significant implications for health policy.

1.3.3 Study #3 - Association Between Attending Physicians' Rates of Referral to Palliative Care and Location of Death in Hospitalized Adults with Serious Illness: A Population-Based Cohort Study

Importance: Patients who receive palliative care are less likely to die in hospital. The role of physician variations in referral to palliative care is unknown.

Objective: To measure the association between physician rates of referral to palliative care and location of death in hospitalized adults with serious illness.

Research Design: Population-based decedent cohort study using linked health administrative data in Ontario, Canada.

Subjects: 7,866 physicians paired with 130,862 hospitalized adults in their last year of life who died of serious illness between 2010 and 2016.

Exposure: Physician annual rate of referral to palliative care (high, average, low).

Measures: Odds of death in hospital versus home, adjusted for patient characteristics.

Results: There was nearly 4-fold variation in the proportion of patients receiving palliative care during follow-up based on attending physician referral rates: high 42.4% (n=24,433), average 24.7% (n=10,772), low 10.7% (n=6,721). Referral to palliative care was also associated with being referred by palliative care specialists and in urban teaching hospitals. The proportion of patients who died in hospital according to physician referral rate were 47.7% (high), 50.1% (average), and 52.8% (low). Hospitalized patients cared for by a physician who referred to palliative care at a high rate had lower risk of dying in hospital than at home compared to patients who were referred by a physician with an average rate of referral (adjusted odds ratio 0.91 (95% CI 0.86 to 0.95); number needed to treat (NNT) = 57 (IQR 41 to 92)) and by a physician with a low rate of referral (adjusted odds ratio 0.81 (95% CI 0.77 to 0.84); NNT = 28 patients (IQR 23 to 44)).

Conclusions and Relevance: An attending physicians' rates of referral to palliative care is associated with a lower risk of dying in hospital. Therefore, patients who are cared for by physicians with higher rates of referral to palliative care are less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation as a barrier to access.

1.4 Thesis Methods

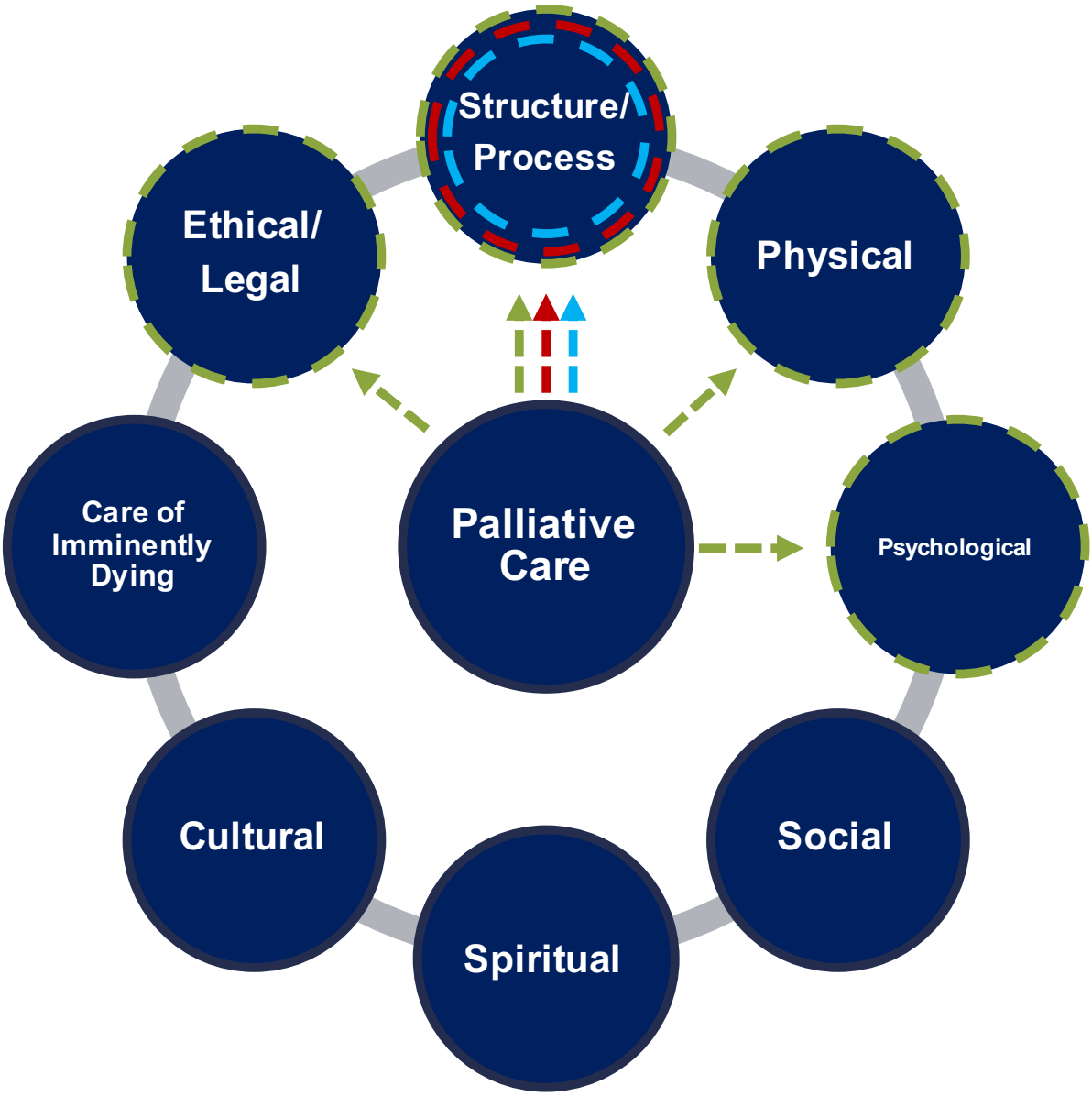
1.4.1 Perspective

This thesis employs a Positivist lens. Positivism is a philosophical theory exploring our understanding of knowledge of things that are not true by their very definition. Positivism holds that all knowledge must be gained *a posteriori*, is exclusively derived from experience of natural phenomena and is interpreted through reason and logic. Further, its supporters believe that theory and observation should serve as the foundations of the scientific method. Ultimately, modern Positivism acknowledges the influence of observer bias and structural limitations on our experience of natural phenomena and our understanding of knowledge. This form of positivism is generally equated with "quantitative research" and carries no explicit theoretical or philosophical commitments.[76]

1.4.2 Structural Framework

The work presented herein is based upon the structural framework of palliative care as outlined in the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care.[77] The guidelines outline the following 8 domains that capture the fundamental principles of palliative care that should be integrated into the care of seriously ill patients: 1) structure and process; 2) physical; 3) psychological and psychiatric; 4) social; 5) spiritual, religious, and existential; 6) cultural; 7) care of the patient nearing the end of life; and 8) ethical and legal (Figure 1).

Figure 1.1 – **Structural framework**. The thesis work herein is based upon the 8 domains of palliative care as outlined in the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care.[77] Study #1 (systematic review, green dashed line) measured the association between palliative care and acute healthcare use, quality of life (QOL), symptom burden and advanced care planning in adults with chronic noncancer illnesses. Study #2 (matched cohort study, blue dashed line) measured the association between newly initiated palliative care in the last 6 months of life, healthcare use and location of death in adults dying from noncancer illness. Study #3 (cohort study, red dashed line) measured the association between physician rates of referral to palliative care and location of death in hospitalized adults with serious illness. Given my interest in both patient- and policy-facing outcomes, my research focused on several domains to inform both aspects of healthcare delivery.


Structure/
Process
Ethical/
Legal
Physical
Palliative
Care
Care of
Imminently
Dying
Psychological
Cultural
Social
Spiritual

1.4.3 Theoretical Framework

A strong theoretical framework is used to help understand the relationships under study, and to guide methodology. I quickly realized that palliative care was a potential mediator on the path to achieving high-value end-of-life care. Palliative care may be one effective means of many to achieve value for patients at the end of life. To aid in the understanding of the relationships under study, the thesis work presented here is framed within the Theory of Value.[78]

Value can be characterized as "agent-relative" (i.e. relative to the patient), and not "agent-neutral". Value is not a description of an overall state of affairs. The Theory of Value stresses the importance of patient choice and the patient's notion of the "highest good". It proposes that the goal of *medicine* (and not health policy) is the good of the whole patient. Value, therefore, is not defined as an overall "good" state of affairs, or as something "good" all things considered. Instead, value can be thought of as what is good for the individual patient. Since value is often used to aid in decision making about allocation of constrained resources, the Theory of Value concludes that traditional health economic frameworks of value (health outcomes divided by costs) can be properly involved in clinical medical decision-making only when those values are part of the individual patient's view of the good.

The Theory of Value and its characterization of the "patient good" has four distinct hierarchical components related to the patient's notion of the "highest good". First is the notion of *biomedical good.* This is an important scientific or technical notion that is not equivalent to the practice of medicine per se. The ability of an opioid to reduce pain or relieve dyspnea are examples of the properties of an intervention to

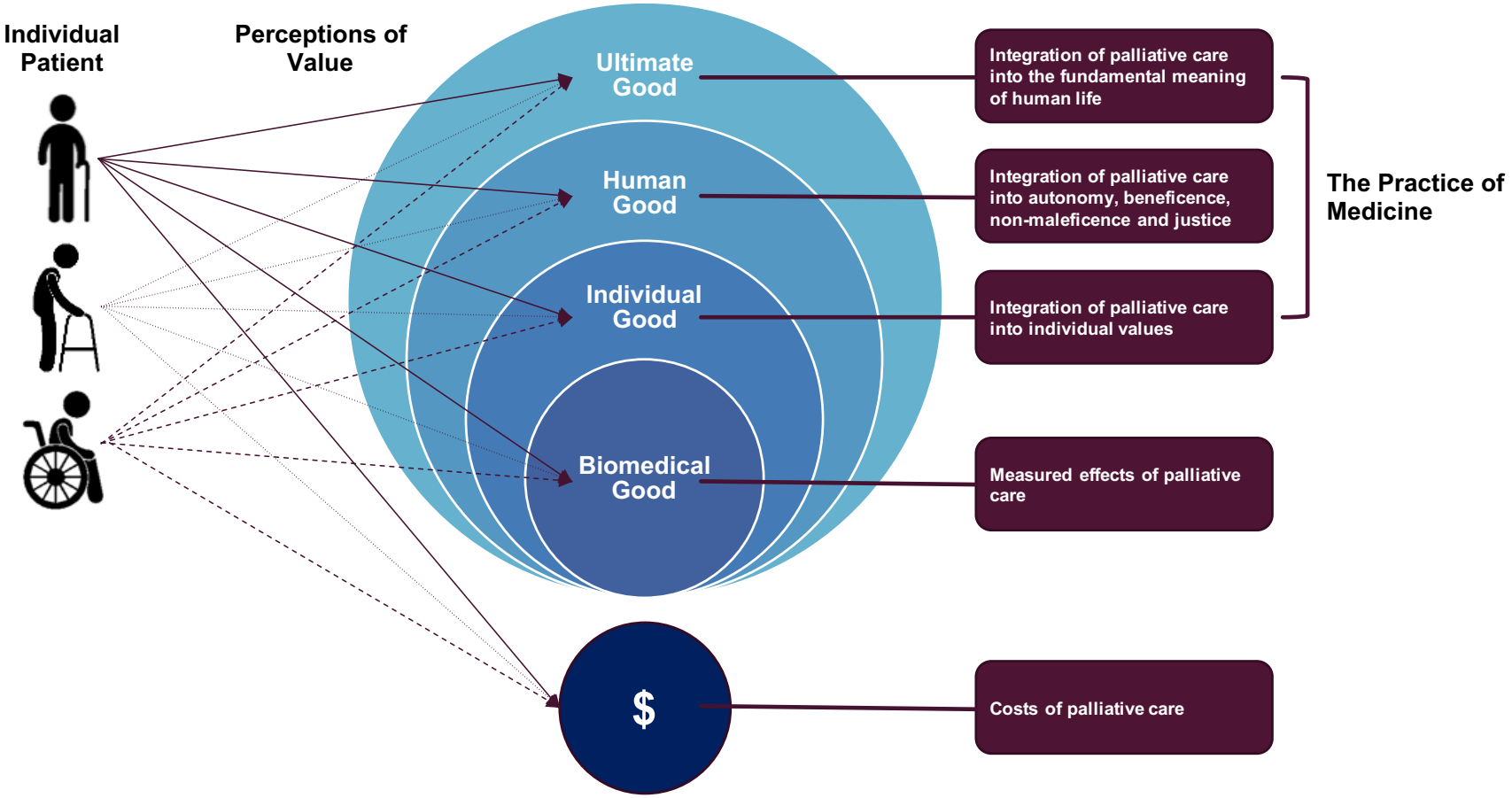
improve the biomedical good of the patient. Second is the notion of the *patient's perception of the good in terms of individual choices and values*. Here, only the patient can evaluate the risks and benefits (i.e., the biomedical good) of a particular medical decision and decide if it is good for *them* (such as whether to take particular medicine, whether to undergo a surgical procedure, or whether to agree to future resuscitation efforts). Third, is the notion of the *patient's good as to what is good for human beings.* This component of value takes a broader perspective beyond the individual, to humans as an entity. Here, the essential principles of medical ethics – autonomy, beneficence, non-maleficence, and justice – are foundational, since these principles deal with what is good for human beings in general. This level of the "good" reflects the desire to respect and treat all humas with dignity because one wants to and not because it will help achieve or accomplish something else. Fourth is the notion of the *ultimate or spiritual good*. This somewhat abstract concept relates to the fundamental meaning of human life, which may or may not be defined in a religious sense.

The Theory of Value states that the practice of medicine serves this hierarchy. As such, medical care is applicable to a wide range of individual values. These values are determined by each patient as to what is biomedically good, what they individually desire as far as their healthcare is concerned, what is good for them as a person and human being, and perhaps most importantly, to whatever their notion of the "highest good" might be. It also posits that value may be individually viewed as "therapeutic parsimony – doing the right amount to achieve the desired outcome, no more and no less".[78] Costs therefore can be a relevant consideration that may directly impact the

patient when making decisions about value, depending on the relative importance they assign to costs.

Using this theoretical framework, the Theory of Value helps in the interpretation of the findings of this thesis and guided the development of the work throughout. Fundamentally, the main objectives of the work focussed on defining the biomedical good of palliative care - its effects on quality of life, symptom burden, location of death and healthcare use as an intervention. However, the Theory of Value is particularly germane to the interpretation and application of these findings to patient care and health policy. How the value of gains in life extension and gains in health-related quality of life are perceived by patients and society at end of life directly impact upon decisions to involve palliative care and its identified benefits and limitations. Ultimately, an understanding of how value fits into the context of the “patient good” will inform the development of new models of palliative and end-of-life care that serve to achieve this good. The challenge for healthcare systems lies in identifying and measuring the ability of new care models to achieve this good.

Figure 1.2 – **Theoretical framework based on the Theory of Value**.[78] Value is framed relative to the patient and is not a description of an overall state of affairs. The theory stresses the importance of patient choice and the patient's notion of the "highest good", with the goal of medicine being the good of the whole patient. It has four distinct hierarchical components related to the patient's notion of the "highest good" and can also considers costs of care to the patient. This framework is individually integrated into a patient's perception of value, which lends itself to the existence of a wide range of individual views.


Individual Patient
Perceptions of Value
Ultimate Good
Human Good
Individual Good
Biomedical Good
$
Integration of palliative care into the fundamental meaning of human life
Integration of palliative care into autonomy, beneficence, non-maleficence and justice
Integration of palliative care into individual values
Measured effects of palliative care
Costs of palliative care
The Practice of Medicine

2 Study #1 – Association of Receipt of Palliative Care Interventions with Healthcare Use, Quality of Life, and Symptom Burden Among Adults with Chronic Noncancer Illness: A Systematic Review and Meta-analysis

2.2 Key Points

Question: Is receipt of palliative care interventions associated with lower acute healthcare use and better patient-centred outcomes in adults with noncancer illness?

Findings: In this systematic review and meta-analysis of 28 randomized clinical trials of patients with primarily noncancer illness, receipt of palliative care interventions, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, but there was no significant difference in quality of life.

Meaning: Among patients with primarily noncancer illness, receipt of palliative care interventions was associated with lower acute healthcare use and modestly lower symptom burden, although analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit generalizability of these specific findings to other chronic illnesses.

2.3 Abstract

Importance: The evidence for palliative care exists predominantly for patients with cancer. The effect of palliative care on important end-of-life outcomes in patients with noncancer illness is unclear.

Objective: To measure the association between palliative care and acute healthcare use, quality of life (QOL) and symptom burden in adults with chronic noncancer illnesses.

Data Sources: MEDLINE, EMBASE, CINAHL, PsychINFO and PubMed from inception to April 18, 2020.

Study Selection: Randomized clinical trials of palliative care interventions in adults with chronic noncancer illness. Studies involving ≥50% of patients with cancer were excluded.

Data Extraction and Synthesis: Two reviewers independently screened, selected and extracted data from studies. Narrative synthesis was conducted for all trials. All outcomes were analyzed using random-effects meta-analysis.

Main Outcome and Measures: Acute healthcare use (hospitalizations and emergency department use), disease-generic and disease-specific quality of life (QOL) and symptoms, with estimates of QOL translated to units of the Functional Assessment of Chronic Illness Therapy scale (FACIT-Pal, range, 0-184 [worst-best]; minimal clinically important difference [MCID], 9 points) and symptoms translated to units of the Edmonton Symptom Assessment Scale global distress score (ESAS, range, 0-90 [best-worst]; MCID, 5.7 points).

Results: Twenty-eight trials provided data on 13,664 patients (mean age 74 years, 46% female) (heart failure, 10 trials, n=4,068 patients; mixed disease, 11 trials, n=8,119 patients; dementia, 4 trials, n=1,036 patients; chronic obstructive pulmonary disease, 3 trials n=441 patients). Palliative care, compared with usual care, was significantly associated with lower ED use (9 trials, n=2,712, 20% versus 24%; odds ratio (OR) 0.82; 95% CI 0.68,1.00, I^2 = 3%), hospitalization (14 trials, n=3,706, 38% versus 42%; OR 0.80; 95% CI 0.65,0.99, I^2 = 41%) and modestly lower symptoms (11 trials, n=2,598, standardized mean difference (SMD) -0.17; 95% CI -0.27,-0.06, I^2 = 0%; ESAS mean difference -2.2; 95% CI -3.6, -0.8). Palliative care was not significantly associated with disease-generic QOL (6 trials, n=1,334, SMD 0.18; 95% CI -0.24,0.61, I^2 = 87%; FACIT-Pal mean difference 4.7; 95% CI -6.3,15.9), or disease-specific measures of QOL (11 trials, n=2,204, SMD 0.07; 95% CI -0.09,0.23, I^2 = 68%).

Conclusions and Relevance: In this systematic review and meta-analysis of randomized clinical trials of patients with primarily noncancer illness, palliative care, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, but there was no significant difference in quality of life. Analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit generalizability to other chronic illnesses.

2.4 Introduction

Chronic noncancer illness such as heart failure (HF), chronic obstructive pulmonary disease (COPD) and dementia are common and associated with high healthcare use, symptom burden, disability and reduced quality of life.[3,5,7–9,11] Palliative care focusses on improving quality of life, reducing suffering and helping with decision making for patients with serious illness and their caregivers.[69] Current evidence for the benefits of palliative care exist predominantly for patients with cancer. Yet there are twice as many patients with noncancer illness and palliative care needs than there are for those with cancer.[79] Application of current evidence for palliative care to those with noncancer illness may therefore restrict its applicability since these chronic diseases have a very different illness trajectory.[65,80–82]

Three recent systematic reviews of randomized clinical trials (RCT) of palliative care interventions reported associations with higher patient and caregiver quality of life (QOL) and lower symptom burden.[69–71] However, more than two-thirds of the trials in these reviews involved patients with cancer, leaving knowledge gaps and uncertainty regarding the potential benefits of palliative care in patients with noncancer illness.

This study measured the association between palliative care and healthcare use, disease-generic and disease-specific measures of QOL and advance care planning for patients with noncancer illness. In addition, it estimated the associated benefit of home-based palliative care, the presence of a physician and an interprofessional palliative care team for multiple important patient-oriented outcomes.

The objective of this study was to conduct a systematic review of palliative care RCTs and to measure the association between palliative care and acute healthcare use, quality of life, symptom burden in adults with noncancer illness.

2.5 Methods

This study was a protocol-based systematic review and meta-analysis (PROSPERO ID: CRD42019127835) conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the preferred reporting items for systematic review and meta-analysis (PRISMA) statement 27-item checklist.[83]

Identification and Selection of Studies

The following databases were searched MEDLINE, EMBASE, CINAHL, PsychINFO and PubMed from inception to April 18, 2020. The primary author (K.L.Q.) and a health sciences librarian (D.H.) conducted the searches (eText 2.1). Two of the reviewers (K.L.Q and M.S.) screened other resources including web searching and bibliographic references from retrieved papers of interest for additional studies not identified by the original search strategy. Pediatric and non–English-language articles were excluded.

Study Eligibility and Inclusion/Exclusion Criteria

Two reviewers (K.L.Q and M.S.) independently evaluated all records for eligibility based on predefined criteria (eTable 2.1). RCTs with a palliative care intervention were included for full review if they were conducted in adults (≥18 years) with a primary diagnosis of heart failure, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), dementia, cirrhosis or stroke. These diseases represent the most common terminal noncancer conditions and are also the most well-studied in palliative care. [69–71] Trials that enrolled multiple groups of patients each with different primary

diseases were categorized as ‘mixed disease’. Since many patients included in palliative care trials may also have cancer, studies that included ≥50% of patients with co-morbid terminal cancer were excluded. Trials of palliative care interventions selected for full review were subsequently included (regardless of whether or not they included specialized palliative care clinicians) if they contained elements of care that addressed ≥2 of 8 domains as outlined in the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care.[77] The NCP guidelines outline eight domains that capture the fundamental principles of palliative care that should be integrated into the care of seriously ill patients. The 8 domains are: structure and process; physical; psychological and psychiatric; social; spiritual, religious and existential; cultural; care of the patient nearing the end of life; and ethical and legal. Eligible studies were required to include ≥2 domains to avoid inclusion of isolated interventions such as therapies for dyspnea or depression, or education for patients and their caregivers and to maintain consistency with prior systematic reviews.[69] Studies that reported on at least 1 of 4 outcomes of interest were included: healthcare use (hospitalizations or emergency department use), QOL (disease-generic or disease-specific measures), and symptom burden. There were no restrictions on the types of comparators.

Data Extraction and Risk of Bias Assessment

Two reviewers (K.L.Q and M.S.) independently extracted data in duplicate from all primary and secondary sources related to a trial using a customized form that was initially piloted for usability. Disagreements were resolved through consensus. All studies were assessed for their risk of bias using the Cochrane Collaboration’s Risk of

Bias tool version 2.[84] The tool uses a series of questions within a set of domains of bias that assess a trial's design, conduct, and reporting. Within each domain, the risk of bias was independently assessed by two reviewers (K.L.Q and K.G.). The tool arrives at a proposed judgement about the trial's overall risk of bias that can be expressed on the extremes as having a 'Low' or 'High' risk of bias, or as an intermediary between the two by having 'Some Concerns' about the risk of bias for an individual trial (eText 2.2). This study included both objective (e.g. hospitalizations, emergency department use) and subjective (e.g. patient-reported quality of life and symptom measures) outcomes. Each type of outcome was assessed separately with respect to its risk of bias to be able to more accurately assign a specific risk for the purposes of the sensitivity analyses for those outcomes. Two summary risk of biases for each trial were reported. Trial authors were contacted to obtain additional data and clarify any questions about a trial's design, conduct, or risk of bias.

Outcomes

The primary outcomes were acute healthcare use (emergency department [ED] use and hospitalization), QOL and symptom burden. To be included in the meta-analysis, data from each trial was required to be reported as the proportion of patients with an ED visit or hospitalization during follow-up or as the mean and standard deviation of quality of life or symptoms scores at baseline and end of study follow-up (range 1-13 months). Healthcare use was analyzed as the proportion of people with ≥1 ED visit or hospitalization during follow-up because access to patient-level data to account for individual follow-up time was not available. Because there is wide variation

in trial design and in the scales used between trials to measure QOL and symptom burden, pooled effects were summarized as standardized mean differences (SMD) corrected for scale directionality, calculated using a Hedges adjusted *g* estimator to correct for small sample bias (eText 2.3).[85] The SMD is a method used to report intervention effects in standardized units, rather than the original units of measurement for each scale. It has been previously proposed that an SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[86] To help with clinical interpretation, SMDs were translated to a common QOL or symptom scale by multiplying the SMD measures from this study with the among-person standard deviation for the specific scale from an RCT of a palliative intervention in patients with advanced heart failure (eText 2.3). The SMD from the QOL outcomes were translated to the Functional Assessment of Chronic Illness Therapy – Palliative (FACIT-Pal, range, 0-184 [worst-best]; minimal clinically important difference [MCID], 9 points) scale - a validated patient-reported measure of QOL in people with serious illness.[87] For measures of symptom burden, the SMDs were translated to the Edmonton Symptom Assessment Scale (ESAS, range, 0-90 [best-worst]; MCID, 5.7 points) – a validated patient-reported measure that is commonly used in palliative populations.[88]

After review of the available data, Advance Care Planning was included as a secondary outcome. Advance Care Planning was defined as a discussion with the patient and/or substitute decision maker that explored preferences for future care, establishing advanced directives and the identification of a substitute decision maker.

Synthesis

A narrative synthesis was performed for all trials to describe the population, their survival and diseases studied, the number of palliative care domains addressed and the nature of the interventions or comparator groups, including the number of studies that included a specialized palliative care physician as part of the intervention.[89] Median survival time could not be measured because access to patient-level data to account for individual follow-up time was not available.

Outcomes were pooled using a random-effects model including a random study effect to account for statistical heterogeneity among studies.[90] Heterogeneity among studies was tested using the I^2 test, and the magnitude of the variation between studies was determined using τ^2. An $I^2 > 50\%$ is considered to represent significant heterogeneity that was taken into account when interpreting the findings.[90,91] In meta-analysis, each trial's estimates of effect should vary (due to random error) and result in a symmetric funnel plot that visualizes this variation. If studies that fail to demonstrate an effect are not published, the funnel plot will be asymmetric. Asymmetry in the funnel plots was statistically tested using the Egger test along with visual review (eFigure 2.5).

A set of secondary analyses were performed using meta-regression to statistically evaluate whether the overall association between palliative care and outcomes was explained by a difference in follow-up time of ≤ 3 months compared to >3 months,[69] the presence or absence of a specialized palliative care physician to provide direct or indirect support to the patient as part of the palliative care intervention,[92] and the specific disease type across all studies. Because access to patient-level data to account for individual follow-up time was not available, overall trial follow-up time was stratified into ≤3 months and >3 months (range 1-13 months) as these timeframes were

considered clinically relevant.[69] Outcome measures were recorded using the longest available follow-up time for studies that reported outcomes for both time periods.

Other secondary analyses quantified the magnitude of the association between palliative care and the primary outcomes within subsets of trials that: 1) excluded studies involving patients with a primary diagnosis of dementia and cancer (i.e. that were enrolled in trials of mixed diseases) as these are recognized as having unique trajectories of functional decline and may influence a person's healthcare needs and subsequent use;[65,80–82] 2) used a palliative care intervention involving an interdisciplinary care team; and 3) used a palliative care intervention involving home-based palliative care, since there is evidence to support its efficacy using both of these approaches.[46,93–95] An interdisciplinary care team was defined as having at least 1 clinician from 2 different health disciplines. This type of analysis is more appropriate when there are fewer studies and statistical testing is therefore limited.[91] Pre-defined sensitivity analyses limited to trials at low-risk of bias were performed on all outcomes where a sufficient number of trials made it possible.

Statistical significance was determined using two-sided error threshold of 0.05. Because of the potential for type 1 error due to multiple comparisons, the findings of these analyses should be interpreted as exploratory. All analyses were conducted using R version 3.1.2.

2.6 Results

Study Characteristics

There were 12,538 unique records identified from the literature search, of which 60 were deemed eligible for full review. A total of 28 trials containing 13,664 patients (mean age 74, 46% female) were included in the final analysis (Figure 2.1). Ten trials (36%) were in patients (n=4,068) with a primary diagnosis of HF,[96–105] 11 (39%) were in patients (n=8,119) with mixed disease (i.e. enrolled multiple groups of patients each with different primary diseases),[106–116] 4 (14%) were in patients (n=1,036) with a primary diagnosis of dementia,[117–120] and 3 (11%) were in patients (n=441) with a primary diagnosis of COPD.[121–123] The pooled prevalence of specific chronic diseases reported across all trials (including those that excluded a specific disease such as cancer) as either primary or co-morbid diagnoses were as follows: HF (65%, n=19 trials), COPD (42%, n=14 trials), stroke (14%, n=9 trials), diabetes (42%, n=8 trials), chronic kidney disease (23%, n=5 trials), and cancer (16%, n=17 trials). Across all studies, 24.3% (SD 26.4%) of patients died. Fourteen trials (50%) were conducted in the outpatient setting, 10 (36%) on the inpatient setting, and 4 (14%) involved both inpatient and outpatient care. Eighteen (64%) were conducted in the United States, 3 in the United Kingdom (11%), 2 in Canada (7%), 1 in each of Hong Kong, Sweden, Switzerland and Australia (14%), and 1 in multiple countries in Europe (4%). Nineteen trials (68%) involved a specialist palliative care physician as part of the intervention. Twenty-six trials assessed subjective outcomes and twenty-six trials assessed objective outcomes. The risk of bias for each trial is reported in eTables 2.5 and 2.6.

There was a median of 5 (range 2-7) palliative care domains addressed by the interventions. Palliative care interventions involved elements of ongoing case management to help coordinate care ("structure and process" domain, n=25), ongoing interdisciplinary support for unmet palliative care needs such as symptoms ("physical" domain, n=22) and emotional ("psychological and psychiatric" domain, n=20) or spiritual distress ("spiritual, religious, and existential" domain, n=17), facilitated discussions to help define goals of care and advance care planning ("ethical and legal" domain, n=20) and addresses environmental and social factors related to care ("social" domain, n=27), and care at the end of life ("care of the patient nearing the end of life" domain, n=5). No studies specifically addressed cultural factors related to care ("cultural" domain, n=0). All trials used usual care as the comparator group. Some elements of usual care included a pre-hospital discharge referral to palliative care,[100] telemonitoring,[99] *ad hoc* visits in a clinic or from a home-visiting general practitioner or palliative care physician,[98,100,104] or education on diet, exercise, advanced care planning and palliative care (eTables 2.2-2.4).[103,109]

Acute Healthcare Use

Emergency department use was assessed in 10 trials; 8 were at high-risk of bias and 2 were at some concerns risk of bias. Six trials involved patients with mixed diseases, 2 with HF and 2 with dementia.[96,105,106,108,111–113,116,118,120] Nine studies (n=2,712 patients) could be pooled in meta-analysis because 1 study reported data in a format that was not possible to include. [96,105,106,108,111,112,116,118,120] In the primary analysis, palliative care was significantly associated with a lower ED use (20% [95% CI

12,28] versus 24% [95% CI 13,34] with ED use; odds ratio (OR) 0.82; 95% CI 0.68,1.00, I^2 = 3%) (Figure 2.2). In the secondary meta-regression analysis, the presence of a palliative care physician significantly explained some of the observed differences in ED use, whereas there was no significant association with heart failure, mixed conditions, dementia or follow-up time (eTable 2.7). In analyses limited to trials of palliative care interventions involving an interdisciplinary care team (OR 0.87; 95% CI 0.72,1.06) and home visits (OR 0.85; 95% CI 0.66,1.08), and among the subset of trials that excluded studies involving patients with a primary diagnosis of dementia (OR 0.77; 95% CI 0.59,1.01) and cancer (OR 0.82; 95% CI 0.63,1.07), the association with lower ED use was not significant (eFigure 2.1, eTable 2.7). An analysis of ED use restricted to trials at low risk of bias could not be performed as none existed.

Hospitalization was assessed in 15 trials; 6 were at high-risk of bias, 5 were at low-risk of bias and 4 were at some concerns risk of bias. Four trials involved patients with mixed diseases, 8 with HF, 3 with dementia and 1 with COPD.[96,98,100–102,104–106,108,111–113,118–120] Fourteen studies (n=3,706 patients) could be pooled in meta-analysis because 1 study reported data in a format that was not possible to include.[96,98,100,101,104–106,108,111–113,118–120] In the primary analysis, palliative care was significantly associated with lower hospitalization (38% [95% CI 25,50] versus 42% [95% CI 30,54] with hospitalization; OR 0.80; 95% CI 0.65,0.99, I^2 = 41%) (Figure 2.2). In the secondary meta-regression analysis, the presence of a palliative care physician explained some of the observed differences in hospitalization, whereas there was no significant association with heart failure, mixed conditions, dementia, or follow-up time (eTable 2.7). In analyses limited to trials of palliative care interventions involving an

interdisciplinary care team (OR 0.93; 95% CI 0.78,1.11) and home visits (OR 0.77; 95% CI 0.53,1.12), and among the subset of trials that excluded studies involving patients with a primary diagnosis of dementia (OR 0.88; 95% CI 0.74,1.05) and cancer (OR 0.90; 95% CI 0.76,1.06), the association with lower hospitalization was not significant (eFigure 2.1, eTable 2.7). When the analysis of hospitalization was restricted to trials at low risk of bias, the association was not significant (OR 0.86; 95% CI 0.68,1.10) (Figure 2.2).

Quality of Life

Quality of life was assessed using disease-generic measures in 8 trials; 6 trials were at high-risk of bias and 2 trials were at low-risk of bias. Five trials involved patients with HF and 3 with mixed disease.[96,98,100,101,103,107,108,124] Six studies (n=1,334 patients) could be pooled in the disease-generic QOL meta-analysis because 1 study reported data in a format that was not possible to include and 1 study reported only the subscales of outcome measures. [96,100,101,103,107,124] In the primary analysis, palliative care was not significantly associated with higher disease-generic measures of QOL, although significant heterogeneity was observed (pooled SMD 0.18; 95% CI -0.24,0.61, I^2 = 87%; FACIT-Pal mean difference 4.7; 95% CI -6.3,15.9) (Figure 2.3). In the secondary meta-regression analysis, the presence of a palliative care physician explained some of the observed differences in disease-generic QOL, whereas there was no significant association with heart failure, mixed conditions, or follow-up time (eTable 2.7). In analyses limited to trials of palliative care interventions involving an interdisciplinary care team (pooled SMD 0.18; 95% CI -0.29,0.64) and home visits

(pooled SMD 0.15; 95% CI -0.40,0.70), and among the subset of trials that excluded studies involving patients with a primary diagnosis of dementia (pooled SMD 0.18; 95% CI -0.24,0.61) and cancer (pooled SMD 0.19; 95% CI -0.31,0.69), the association with higher disease-generic QOL was not significant (eFigure 2.2, eTable 2.7). When the analysis of disease-generic QOL were restricted to trials at low risk of bias, there was a significant association with higher and clinically significant measures of QOL (SMD 0.37; 95% CI 0.02,0.71, I^2 = 22%, FACIT-Pal mean difference 9.7; 95% CI 0.5,18.5) (Figure 2.3).

Quality of life was assessed using disease-specific measures in 12 trials; 6 were at high-risk of bias and 6 trials were at low-risk of bias. Eight trials involved patients with HF, 2 with mixed disease, 1 with dementia and 1 with COPD.[98–105,107,110,120,122] Eleven studies (n=2,204 patients) could be pooled in the disease-specific QOL meta-analysis because 1 study reported data in a format that was not possible to include.[98–105,107,110,120] In the primary analysis, palliative care was not significantly associated with disease-specific measures of QOL (pooled SMD 0.07; 95% CI -0.09,0.23, I^2 = 68%), although substantial heterogeneity was observed. In the secondary meta-regression analysis, there was no significant association with the presence of a palliative care physician, heart failure, mixed conditions or follow-up time (eTable 2.7). In the other secondary analyses, interventions involving an interdisciplinary care team (SMD 0.15; 95% CI 0.02,0.29, I^2 = 28%) and home visits (SMD 0.37; 95% CI 0.05,0.69, I^2 = 35%) was significantly associated with higher disease-specific measures of QOL. There was a significant association observed when excluding trials of dementia (SMD 0.13; 95% CI 0.01,0.25, I^2 = 10%) or cancer (SMD 0.12; 95% CI 0.00,0.23, I^2 = 12%) (eFigure 2.2,

eTable 2.7). When the analysis of disease-specific QOL were restricted to trials at low risk of bias, no significant association was observed (SMD 0.17; 95% CI -0.09,0.43, I^2 = 68%)(Figure 2.3).

Symptoms

Symptoms were assessed in 14 trials; 9 were at high-risk of bias, 4 were at low-risk of bias, and 1 was at some concerns risk of bias. Six trials involved patients with HF, 6 with mixed disease and 2 with dementia.[98–100,102–104,106,107,109,110,112,117,118,121] Eleven studies (n=2,598 patients) could be pooled in meta-analysis because 3 studies reported data in a format that was not possible to include.[98–100,102–104,106,107,109,110,112,117,121] In the primary analysis, palliative care was significantly associated with lower symptoms (pooled SMD -0.12; 95% CI -0.20,-0.03, I^2 = 0%; ESAS mean difference -1.6; 95% CI -2.6,-0.4), which would translate to an average of a 0.2 point decrease across all subdomains on the ESAS (Figure 2.4). In the secondary meta-regression analyses, the presence of a palliative care physician, heart failure, and mixed conditions explained some of the observed difference in symptoms whereas there was no significant association with follow-up time (eTable 2.7). In the other secondary analyses, interventions involving an interdisciplinary care team was significantly associated with lower symptoms (SMD -0.11 95% CI -0.19,-0.02, I^2 = 0%, ESAS mean difference -1.5; 95% CI -2.5,-0.3). In analyses limited to trials of palliative care interventions involving home visits the association with lower symptoms was not significant (pooled SMD -0.15 95% CI -0.34,0.03). Among the subset of trials that excluded studies involving patients with a primary diagnosis of dementia (pooled SMD -

0.12; 95% CI -0.20,-0.03, I^2 = 0%; ESAS mean difference -1.6; 95% CI -2.6,-0.4) and cancer (pooled SMD -0.16 95% CI -0.31,-0.01, ESAS mean difference -2.1; 95% CI -4.1,-0.1), the association with lower symptoms was significant (eFigure 2.3, eTable 2.7). When the analysis of symptoms were restricted to trials at low risk of bias, no significant association was observed (pooled SMD -0.15 95% CI -0.30,0.01) (Figure 2.4).

Advance Care Planning

Advance Care Planning was assessed in 9 trials; 2 were at high-risk of bias, 4 were at low-risk of bias, and 3 were at some concerns risk of bias. Three trials involved patients with HF, 3 with mixed disease, 2 with COPD and 1 with dementia.[97,102,103,110,114,116,119,122,123] Seven studies (n=5,935 patients) could be pooled in meta-analysis because 2 studies reported data in a format that was not possible to include. [97,103,110,114,119,122,123] In a *post-hoc* analysis, palliative care was significantly associated with Advance Care Planning, although there was considerable heterogeneity (38% [95% CI 25,50] versus 42% [95% CI 30,54] with Advance Care Plan, OR 2.95; 95% CI 1.52,5.73, I^2 = 84%) (Figure 2.5). In the secondary meta-regression analysis, the presence of a palliative care physician, heart failure, COPD, and dementia explained some of the observed differences in advanced care planning, whereas there was no significant association with mixed conditions (eTable 2.7). In the other secondary analyses, interventions involving an interdisciplinary care team was significantly associated with higher Advance Care Planning (OR 3.34 95% CI 2.10,5.29, I^2 = 0%). There were no studies of intervention involving home visits. In analyses among the subset of trials that excluded studies involving patients with a primary diagnosis of

dementia (OR 2.65 95% CI 1.35,5.21) and cancer (OR 3.74 95% CI 2.39,5.83) the association with Advance Care Planning was significant (eFigure 2.4, eTable 2.7). When the analysis of Advance Care Planning was restricted to trials at low risk of bias, a persistent significant association was observed (OR 3.20; 95% CI 2.26,4.54, I^2 = 0%) (Figure 2.5).

2.7 Discussion

In this systematic review and meta-analysis of 28 randomized clinical trials providing data on 13,664 patients with primarily noncancer illness, palliative care was associated with lower healthcare use and modestly lower symptom burden. Although palliative care was associated with higher advance care planning and was not associated with better quality of life, significant heterogeneity between trials in both analyses weakened confidence in these findings. When analyses were restricted to trials at low risk of bias, evidence for higher disease-generic measures of QOL were found. The collective findings from this study will help to define the specific associated benefits of palliative care in noncancer illness, which will inform the ongoing design and delivery of palliative care for patients, their clinicians and policy makers within healthcare systems.

Secondary analyses of potential outcomes associated with palliative care were varied. There were associated benefits of palliative care when there was the presence of a palliative care physician or an interdisciplinary team. These findings may be related to the specific skills and nuanced decision-making about optimal therapies that a palliative care physician may provide to their patients,[125] a responsibility that other clinicians such as nurse practitioners with prescribing abilities can also perform. Since 11 of 28 trials and 38% of patients in all trials had a diagnosis of heart failure, the results may be weighted by the benefits to heart failure patients. However, because heart failure was not the majority condition and there was a considerable mix of disease types in most individual analyses, the findings likely apply to the general population studied. Caution should be exercised when interpreting the QOL outcomes specifically as they

were based predominantly on studies of patients with heart failure, which may limit generalizability of these specific findings to other noncancer illness. This study identified significant knowledge gaps related to the role of palliative care in people with other common noncancer illnesses such as COPD, ESRD, stroke and cirrhosis as there were few to no RCTs for patients with these diseases. Palliative care that provided home-based care was not associated with lower healthcare use or symptoms, or higher measures of quality of life. This is surprising, as hospitalization near the end of life is associated with poor quality of life,[8–10] and 40% of people with serious illness report that they value the health services available to care for them in their home.[23] One possible explanation for these findings are that most patients enrolled in trials of palliative care interventions in this study survived. The strongest benefits for home-based palliative care appears to be for patients who are nearing the end of their life.[46] However, the magnitude of the summary point estimates were similar to the primary analyses, but the confidence intervals wider, which may suggest that these secondary analyses were underpowered to detect a significant difference.

This study specifically highlights that the use of an interdisciplinary team and the involvement of a specialized palliative care physician are associated with better patient-centered outcomes, which may be related to their ability to address the broad range of palliative care needs in people with serious illness.[92,126] The findings from this study support ongoing efforts by healthcare systems and policy makers to expand and optimize the delivery of palliative care to people with noncancer illness by providing evidence for its associated benefits in this population. Future work should seek to better

understand why this may be – and whether other clinicians with prescribing privileges such as nurse practitioners can be equally as effective.

Prior work in this area reported conflicting results. A recently published population-based cohort study demonstrated a significant association between newly initiated palliative care and lower healthcare use including the rates of ED use, hospitalization and ICU admission.[66] Other research that measured the association between palliative care and various measures of healthcare use in noncancer illness reported varying results.[69,98,100–102,104,105,108,111–113,116,118,119] The are 3 recent systematic reviews and meta-analyses—which predominantly included patients with cancer – that examined the role of palliative care on multiple end-of-life outcomes.[69–71] These reviews were unable to perform other meta-analyses for outcomes that relate to the provision of high-value end-of-life care[127] such as healthcare use and advanced care planning due to limitations in the available evidence at the time. The subsequent publication of ten trials of palliative care interventions in patients with noncancer illness served as the impetus to perform these further analyses to address the existing knowledge gaps specifically highlighted by Kavalieratos *et al* in their review.[96–98,103,104,106,118,120,122,124] This study provides updated evidence regarding associations of palliative care interventions with important healthcare use and patient-focused outcomes specifically in patients with noncancer illness.

The lack of association with palliative care and higher quality of life was unexpected. This may be related to significant heterogeneity in the interventions between trials and the substantial influence of the study by Van Spall *et al*. on the outcome, which was found to be at high risk of bias.[96] There was a clinically meaningful

association between palliative care and higher disease-generic measures of quality of life when the analysis was restricted to studies at low risk of bias, which excluded Van Spall *et al*.[96] It may be related to specific differences in incremental benefits between specialist and non-specialist palliative care interventions. Van Spall *et al*. employed a non-specialist palliative care intervention. Differences in important outcomes between specialist and non-specialist palliative care interventions were consistently demonstrated in this study and others.[126] It is also possible that the standard of 'usual' care is incorporating more principles of palliative care over time, leading to smaller differences in non-specialist palliative care interventions with more recently published studies like Van Spall *et al*.[96] Alternatively, the findings may be due to challenges in dealing with a high burden of palliative care needs related to higher healthcare use, worse functional impairments and higher levels of anxiety and depression in these patients when compared to patients with cancer.[128–130]

Limitations

This study has several limitations. First, it excluded other important but far less prevalent conditions such as neurodegenerative disorders (e.g. Parkinson's disease, amyotrophic lateral sclerosis or multiple sclerosis), other chronic lung diseases (e.g. pulmonary fibrosis), rheumatologic disease (e.g. systemic sclerosis, lupus and rheumatoid arthritis) and HIV/AIDS. Second, some trials of mixed conditions included a minority of patients with cancer, which may have influenced the findings. However, sensitivity analyses that specifically excluded trials with some patients who had cancer revealed consistent findings to the primary analyses, which were also of a similar

magnitude. Third, many of the elements of palliative care were also present in usual care, which may underestimate the magnitude of the findings. As palliative care is increasingly recommended earlier in the course of a patient's illness, these effects may be more pronounced over time. Fourth, this study was not restricted to specialized palliative care interventions, but instead included studies employing a "palliative approach" to care.[69] Consequently, the results suggest the expansion of generalist palliative care programs in large healthcare systems may be beneficial given that the current demand for palliative care has outstripped the supply of specialized palliative care clinicians. However, this study, and prior work, has demonstrated additional benefit when care is provided by specialist palliative care clinicians.[45,126] Despite minimal amounts of statistical heterogeneity among studies observed in this meta-analysis, the heterogeneity among palliative care interventions occurring across different jurisdictions may limit its applicability to individual healthcare systems with different definitions and access to palliative care, along with differences in practice patterns for usual care. Further work is needed to delineate potential differences in patient outcomes when comparing care provided by generalist and specialist palliative care teams to understand how best to deploy both to meet the expanding need to care for patients with serious noncancer illness. Fifth, although palliative care was associated with lower symptom burden, it is possible that the burden of specific symptoms was also meaningfully lower but could not be measured without the availability of patient-level data. Sixth, caregiver outcomes were not assessed, which are increasingly recognized as important aspects of providing palliative care in light of the rising rates of caregiver burnout.[131] Seventh, the potential relationship between the presence of Advance Care

Planning and the other study outcomes was not evaluated as this was outside the scope of this study. Eighth, significant questions still remain regarding the optimal timing and care setting in which to initiate palliative care and which models of care will provide the most benefit.[93,94] This may be especially relevant since patients with noncancer illness are more likely to receive palliative care closer to death than in patients with cancer, and the timing of a shift from curative treatment strategies to comfort care is less clear.[65,66]

2.8 Conclusions

In this systematic review and meta-analysis of randomized clinical trials of patients with primarily noncancer illness, palliative care, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, but there was no significant difference in quality of life. Analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit generalizability to other chronic illnesses.

Figure 2.1 – Results of the literature search to identify randomized clinical trials of palliative care interventions.

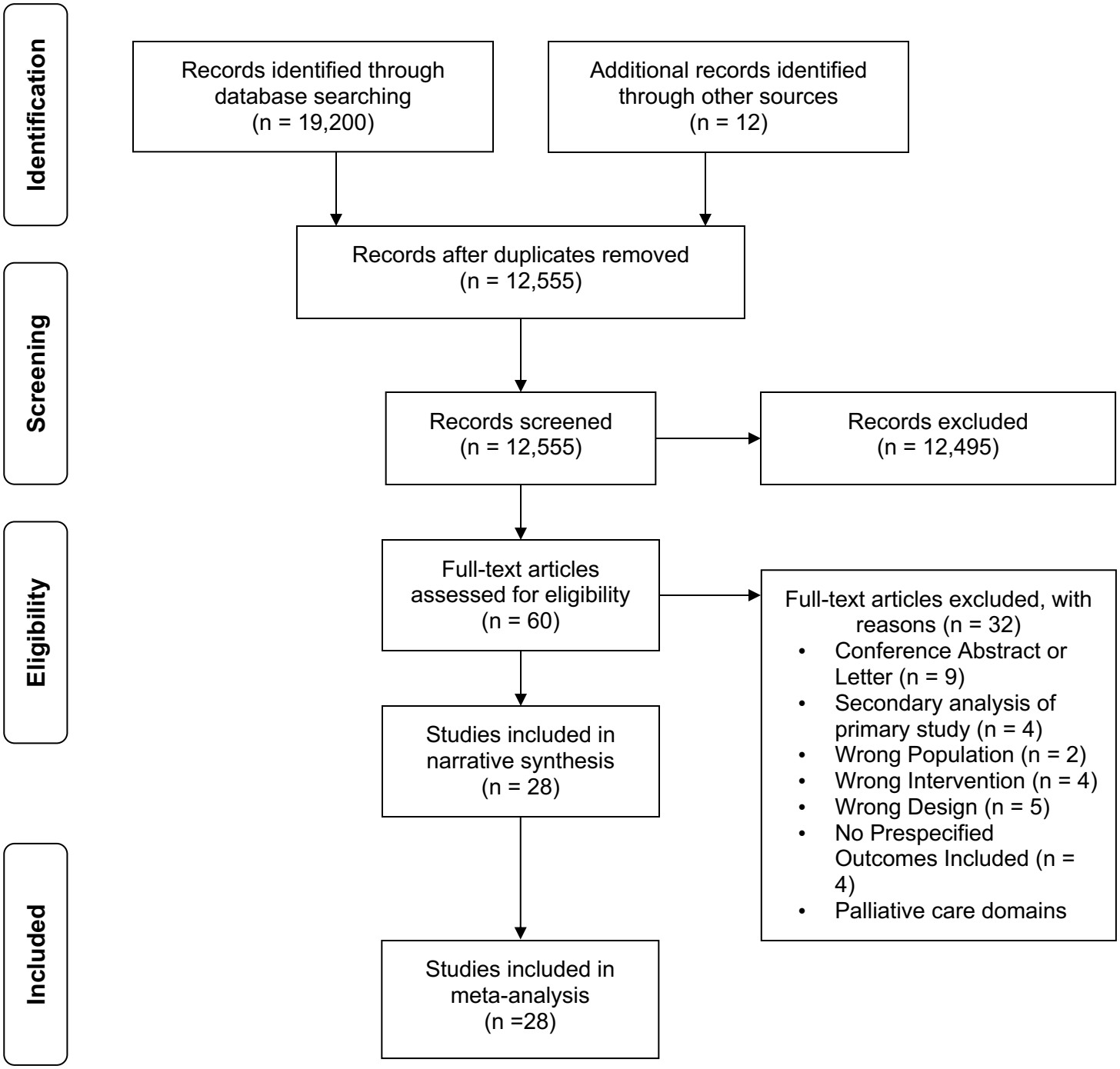
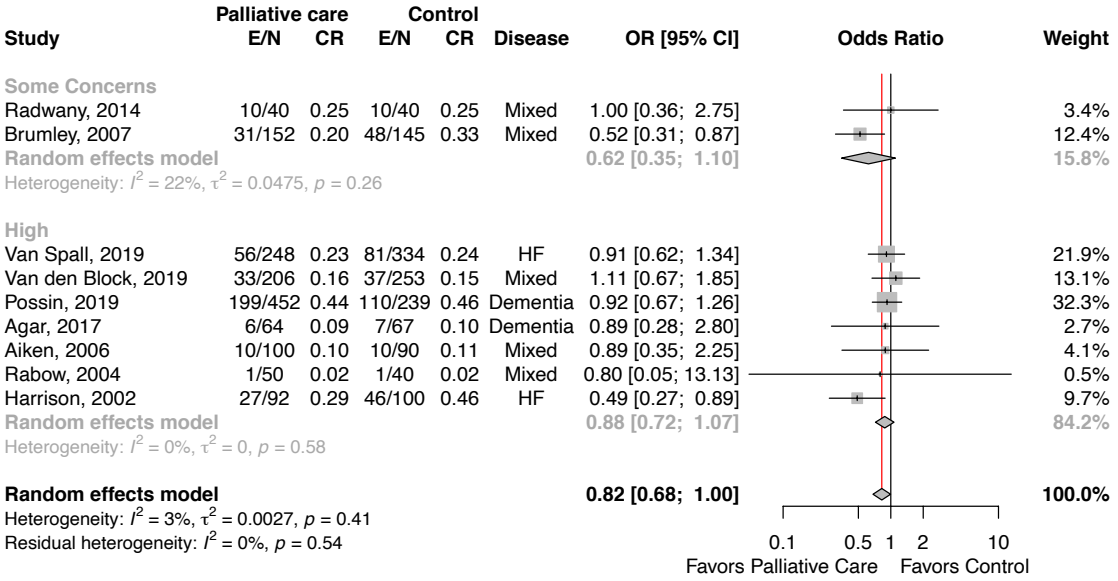


Figure 2.2 – Random-Effects Meta-analysis of the Association Between Palliative Care and Healthcare Use for (A) Emergency department (ED) Use and (B) Hospitalization. Data are presented as the odds and 95% CIs (error bars) of at least one ED use or hospitalization during study follow-up. The area of the shaded squares is proportional to the study weight and the shaded diamonds represent pooled odds and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). E – Events, N – total number of patients in trial, CR – crude rate, HF – heart failure.

A: Emergency Department Use



B: Hospitalization

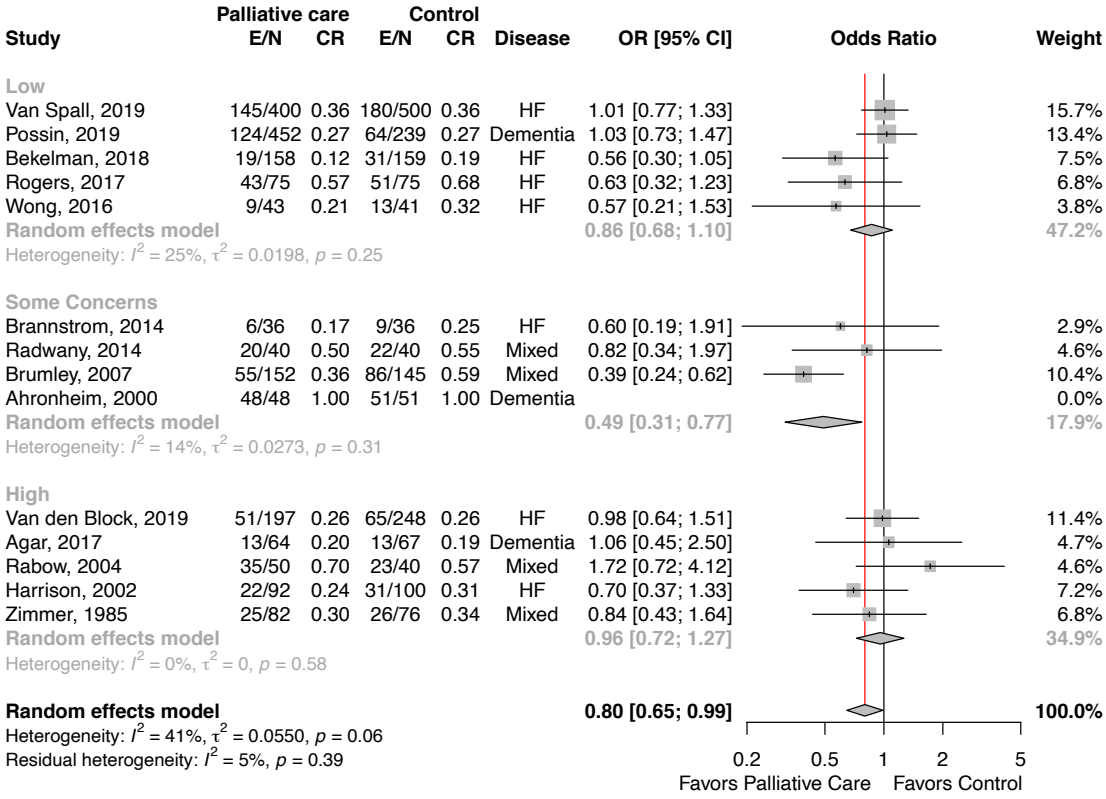
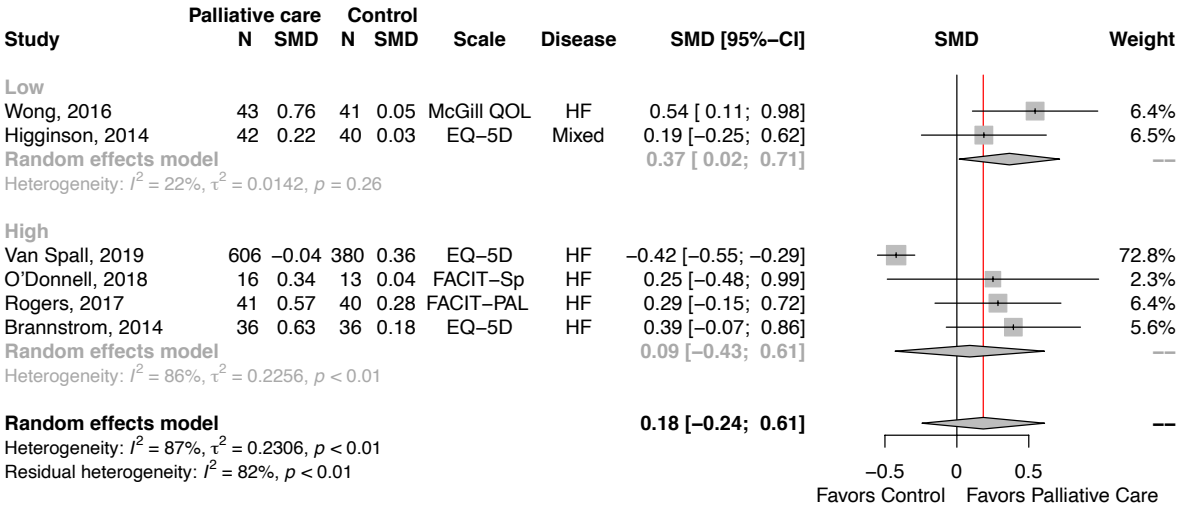


Figure 2.3 – Random-Effects Meta-analysis of the Association Between Palliative Care and (A) Disease-Generic and (B) Disease-Specific Measures of Quality of Life (QOL). Data are presented as the means and 95% CIs (error bars) of the change in quality of life measures from baseline to the end of study follow-up. The area of the shaded squares is proportional to the study weight and the shaded diamonds represent pooled standardized mean difference and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). SMD – Standardized Mean Difference, N – total number of patients in trial, HF – heart failure; EQ-5D – EuroQol-5D; FACIT - Functional Assessment of Chronic Illness Therapy scale; KCCQ – Kansas City Cardiomyopathy Questionnaire; CRQ HRQOL – Chronic Respiratory Questionnaire Health-Related Quality of Life; CHQ-C – Chronic Heart Failure Questionnaire Chinese; MLHFQ – Minnesota Living with Heart Failure Questionnaire.

A: Disease–Generic Measure of Quality of Life



B: Disease–Specific Measure of Quality of Life

Study	Palliative care N	Palliative care SMD	Control N	Control SMD	Scale	Disease	SMD [95%–CI]	Weight
Low								
Possin, 2019	368	−0.19	201	−0.27	QoL–AD	Dementia	0.07 [−0.10; 0.24]	24.3%
Wong, 2016	43	0.78	41	0.05	CHQ–C	HF	0.64 [0.20; 1.07]	3.7%
Bekelman, 2015	164	0.77	167	0.78	KCCQ	HF	0.02 [−0.19; 0.24]	15.5%
Higginson, 2014	42	0.62	40	0.22	CRQ HRQOL	Mixed	0.38 [−0.06; 0.82]	3.8%
Gade, 2008	199	0.78	191	0.80	Self–reported QOL	Mixed	0.04 [−0.16; 0.23]	18.2%
Random effects model							**0.14 [−0.02; 0.31]**	––
Heterogeneity: I^2 = 52%, τ^2 = 0.0171, p = 0.08								
High								
Bekelman, 2018	121	0.29	121	0.15	KCCQ	HF	0.11 [−0.14; 0.37]	11.3%
O'Donnell, 2018	16	0.46	15	0.62	KCCQ	HF	−0.22 [−0.93; 0.49]	1.4%
Rogers, 2017	41	1.34	40	0.94	KCCQ	HF	0.30 [−0.14; 0.73]	3.7%
Sidebottom, 2015	79	0.61	88	0.55	MLHFQ	HF	0.13 [−0.17; 0.44]	7.8%
Brannstrom, 2014	36	2.82	36	1.50	KCCQ	HF	0.07 [−0.39; 0.53]	3.4%
Harrison, 2002	79	−1.00	76	−0.33	MLHFQ	HF	−0.68 [−1.00; −0.35]	6.9%
Random effects model							**−0.04 [−0.35; 0.27]**	––
Heterogeneity: I^2 = 75%, τ^2 = 0.1062, p < 0.01								
Random effects model							**0.07 [−0.09; 0.23]**	––
Heterogeneity: I^2 = 68%, τ^2 = 0.0457, p < 0.01								
Residual heterogeneity: I^2 = 69%, p < 0.01								

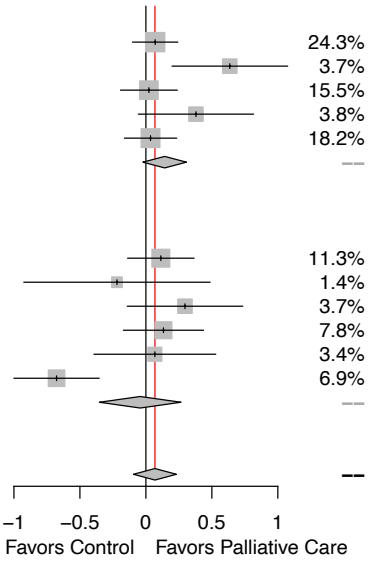


Figure 2.4 – Random-Effects Meta-analysis of the Association Between Palliative Care and Symptoms. Data are presented as the means and 95% CIs (error bars) of the change in symptom measures from baseline to the end of study follow-up. The area of the shaded squares is proportional to the study weight and the shaded diamonds represent pooled standardized mean difference and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). SMD – Standardized Mean Difference, N – total number of patients in trial, HF – heart failure; PHQ – Patient Health Questionnaire; HADS - Hospital Anxiety and Depression Scale; VAS – Visual Analogue Scale; ESAS – Edmonton Symptom Assessment Scale; MCOHPQ - Modified City of Hope Patient Questionnaire.

Symptoms

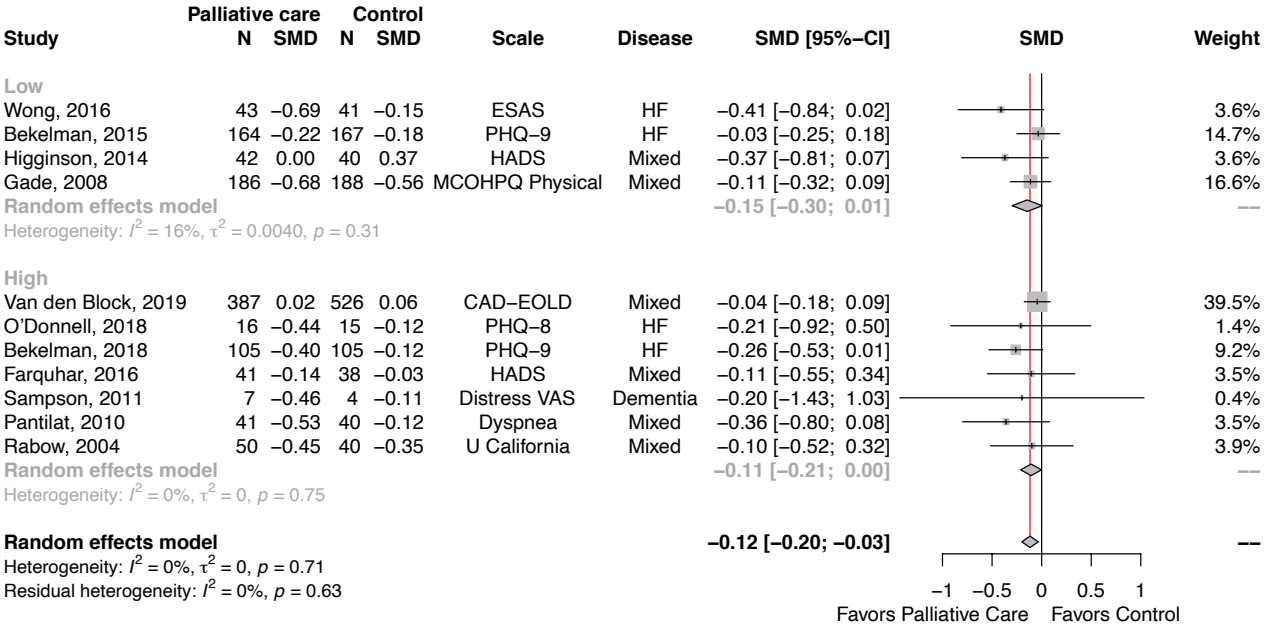
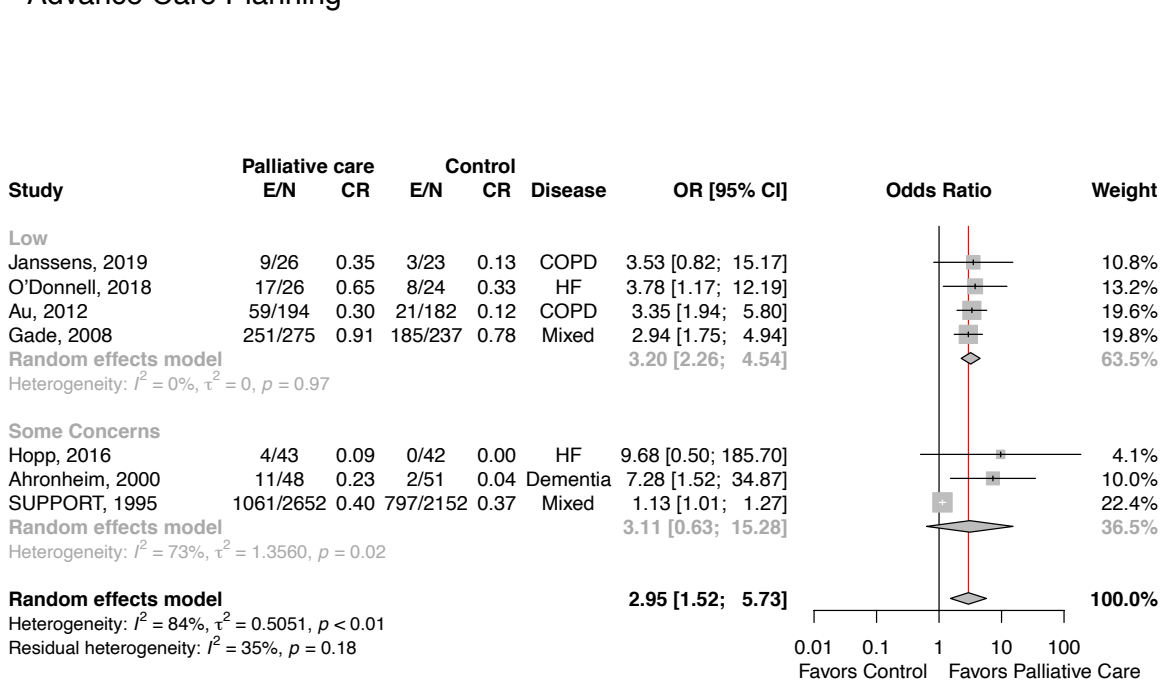


Figure 2.5 – Random-Effects Meta-analysis of the Association Between Palliative Care and Advance Care Planning. Data are presented as the odds and 95% CIs (error bars) of a newly documented advanced care plan during study follow-up. The area of the shaded squares is proportional to the study weight and the shaded diamonds represent pooled odds and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns) Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). E – Events, N – total number of patients in trial, CR – crude rate, HF – heart failure



2.9 Supplementary Online Content

Association of Receipt of Palliative Care Interventions with Healthcare Use, Quality of Life, and Symptom Burden Among Adults with Chronic Noncancer Illness

A Systematic Review and Meta-analysis

eText 2.1 - Methodological Details Regarding Search Strategy

Medline Search Strategy

1. palliative care/ or terminal care/ or hospice care/
2. (palliative or hospice* or (terminal adj3 care)).ti,ab,kf.
3. "Hospice and Palliative Care Nursing"/
4. Hospices/
5. Palliative Medicine/
6. ((End of life or End-of-life) adj3 care).ti,ab,kf.
7. 1-6/OR
8. attitude to death/ or attitude to health/ or health services misuse/ or medical overuse/ or unnecessary procedures/ or "patient acceptance of health care"/ or patient compliance/ or patient dropouts/ or patient participation/ or patient satisfaction/ or patient preference/ or treatment refusal/
9. Health Services/ut [Utilization]
10. hospitalization/ or "length of stay"/ or patient admission/ or patient discharge/ or patient readmission/
11. Life Support Care/ut [Utilization]
12. Hospital Costs/
13. Diagnostic Tests, Routine/ut [Utilization]
14. "Diagnostic Techniques and Procedures"/ut [Utilization]
15. Quality Indicators, Health Care/
16. "Quality of Life"/
17. "costs and cost analysis"/ or health care costs/ or hospital costs/
18. sickness impact profile/
19. depression/ or stress, psychological/
20. Anxiety/
21. treatment outcome/
22. patient satisfaction/ or patient preference/
23. spirituality/
24. FACIT-Pal.ti,ab,kf.
25. functional assessment of chronic illness therapy palliative.ti,ab,kf.
26. (SF36 or SF-36 or short form 36).ti,ab,kf.
27. Kansas City Cardiomyopathy Questionnaire.ti,ab,kf.
28. KCCQ.ti,ab,kf.
29. Minnesota living with heart failure questionnaire.ti,ab,kf. Or MLHFQ.ti,ab,kf.
30. St Georges respiratory questionnaire.ti,ab,kf. Or SGRQ-C.ti,ab,kf.
31. COPD Assessment Test.ti,ab,kf.
32. quality of life in alzheimer's disease.ti,ab,kf.
33. QOL-AD.ti,ab,kf.

34. CHOICE health experience.ti,ab,kf.
35. Choices for healthy outcomes in caring.ti,ab,kf.
36. (Kidney disease quality of life* or KDQOL).ti,ab,kf.
37. parfrey test.ti,ab,kf.
38. (chronic liver disease questionnaire or CLDQ).ti,ab,kf.
39. (short form liver disease quality of life or SF-LDQOL).ti,ab,kf.
40. (Liver disease symptom index or LDSI).ti,ab,kf.
41. (Stroke specific quality of life scale or SSQoL).ti,ab,kf.
42. (stroke impact scale or SIS).ti,ab,kf.
43. (Stroke adapted sickness impact profile or SASIP).ti,ab,kf.
44. patient care planning/ or advance care planning/ or advance directives/ or living wills/
45. (goal* adj3 care).ti,ab,kf.
46. (care adj3 plan*).ti,ab,kf.
47. (advance* adj3 plan*).ti,ab,kf.
48. advance* directive*.ti,ab,kf.
49. power of attorney.ti,ab,kf.
50. (living will or living wills).ti,ab,kf.
51. place of death.ti,ab,kf.
52. home death.ti,ab,kf.
53. end-of-life care.ti,ab,kf.
54. resource allocation/ or health care rationing/
55. (resource* adj3 (allocat* or efficien*)).ti,ab,kf.
56. (healthcare adj3 ration*).ti,ab,kf. or (health care adj3 ration*).ti,ab,kf.
57. exp Death/
58. home death.ti,ab,kf.
59. non-hospital death.ti,ab,kf.
60. (location adj3 death).ti,ab,kf.
61. (attitude* adj3 (death* or health*)).ti,ab,kf.
62. (utiliz* adj3 (healthcare or health care or health service* or life support or test or tests or procedure*)).ti,ab,kf.
63. (Cost* adj3 (hospital or healthcare or health care or test or tests or procedure*)).ti,ab,kf.
64. (accept* adj3 death).ti,ab,kf.
65. ((treatment or patient*) adj3 (adherence or compliance or cooperation)).ti,ab,kf.
66. (length of stay or patient admission or patient readmission).ti,ab,kf.
67. quality of life.ti,ab,kf.
68. (depress* or stress*).ti,ab,kf.
69. anxiety.ti,ab,kf.
70. (treatment outcome* or patient satisfaction or patient preference*).ti,ab,kf.

71. (cost* adj3 (hospital or healthcare or health care or test or tests or procedure*)).ti,ab,kf.
72. 8-71/OR
73. heart failure/ or heart failure, diastolic/ or heart failure, systolic/ or pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/ or kidney failure, chronic/ or frasier syndrome/ or End Stage Liver Disease/
74. ((cardiac or heart or myocardial) adj3 (insufficiency or failure)).ti,ab,kf.
75. (liver failure* adj3 chronic).ti,ab,kf.
76. (liver disease* adj3 end).ti,ab,kf.
77. cirrhosis.ti,ab,kf.
78. exp Dementia/
79. stroke/ or brain infarction/ or brain stem infarctions/
80. ((non cancer* or non-cancer* or noncancer*) adj3 (disease* or diagnosis or patient*)).ti,ab,kf.
81. (dementia* or amentia* or alzheimer*).ti,ab,kf.
82. Tauopathies/
83. tauopath*.ti,ab,kf.
84. cerebrovascular accident.ti,ab,kf.
85. stroke*.ti,ab,kf.
86. ((brain or cerebellum) adj3 infarction*).ti,ab,kf.
87. ((end-stage or end stage) adj3 (kidney or renal)).ti,ab,kf.
88. (chronic adj3 (kidney or renal) adj3 failure).ti,ab,kf.
89. (chronic adj3 airflow obstruct*).ti,ab,kf.
90. copd.ti,ab,kf.
91. ((cardiac or heart or myocardial) adj3 (failure* or insufficiency)).ti,ab,kf.
92. (chronic obstruct* adj3 disease).ti,ab,kf.
93. (heart edema or diastolic dysfunction or systolic dysfunction).ti,ab,kf.
94. ((Cardiac or heart) adj2 (edema or oedema)).ti,ab,kf.
95. Lewy body disease.ti,ab,kf.
96. Senility.ti,ab,kf.
97. Mental deteriorat*.ti,ab,kf.
98. Frasier syndrome.ti,ab,kf.
99. (Heart edema or Diastolic dysfunction or Systolic dysfunction).ti,ab,kf.
100. Dialysis/
101. Hemodialysis/
Renal Dialysis/ or Hemodiafiltration/ or Hemodialysis, Home/ or Peritoneal Dialysis/ or Peritoneal Dialysis, Continuous Ambulatory/
102. (Dialysis or hemodialysis or hemodiafiltration).ti,ab,kf.
103. 73-103/OR
104. 7 AND 72 AND 104

Limits
NOT (adolescent/ or child/ or child, preschool/ or infant/ or exp infant, newborn/) not exp Adult/
NOT exp animal/ not human/
English only
No books, book chapters or dissertations

eText 2.2. Methodological Details Regarding Risk of Bias Assessment

All studies were assessed for their risk of bias using the Cochrane Collaboration's Risk of Bias tool version 2. This tool contains five domains: risk of bias arising from the randomization process; due to deviations from the intended interventions; due to missing outcome data; from measurement of the outcome; or in selection of the reported result. Judgement about the overall risk of bias arising from the five domains was made using the published algorithm based on answers to the signalling questions within the tool. Within each domain, the risk of bias was assessed by two independent reviewers. Judgements could be 'Low', 'High' or 'Some Concerns' risk of bias.

Because our study included both objective (e.g. hospitalizations, emergency department visits) and subjective (e.g. patient-reported quality of life and symptom measures) outcomes, we assessed each separately with respect to their risk of bias. We reported two summary risks of bias for each trial. When assessing the risk of bias for subjective outcomes, we made the following modifications based on recommendations from the Cochrane Collaboration because it is impractical to blind study participants to a complex behavioral intervention such as palliative care:

1. For domain 1, allocation sequences were only considered concealed if a statement was explicitly made regarding concealment or if a computer-generated sequence was used for randomization.
2. For domain 2, we omitted item 2.3 ("*Were important co-interventions balanced across intervention groups?*") from the final judgement decisions because all studies were subject to the risk of unintended co-interventions regardless of whether they were reported or not.
3. For domain 4, items 4.3 (*"Were outcome assessors aware of the intervention received by study participants ?"*), 4.4 (*"Could assessment of the outcome have been influenced by knowledge of intervention received?"*) and 4.5 (*"Is it likely that assessment of the outcome was influenced by knowledge of intervention received?"*) were omitted from final risk of bias judgements for all subjective outcomes as all studies were judged 'High' risk for this domain.

eText 2.3. Translation of Standardized Mean Differences to Clinical Values

For measures of both general and disease-specific quality of life (QOL), we translated the standardized mean difference (SMD) to the Functional Assessment of Chronic Illness Therapy – Palliative (FACIT-Pal) scale - a validated patient-reported measure of QOL in people with serious illness.[1] We used the standard deviation (SD) from a randomized control trial of patients with advanced heart failure (n=150).[2] For measures of symptom burden, we translated the SMD to the Edmonton Symptom Assessment Scale (ESAS) – a validated patient-reported measure that is commonly used in palliative populations.[3] We used the standard deviation (SD) from a multicenter randomized control trial of patients with advanced heart failure (n=84).[4] We intentionally used trials of patients with HF that measured the FACIT-Pal and ESAS because 40% of the trials in this systematic review were in patients with HF.

eTable 2.1 – Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria

• Sample:
  ○ Adults ≥18 years
  ○ Main diagnosis of heart failure, chronic obstructive pulmonary disease, end-stage renal disease, cirrhosis, dementia or stroke
• Intervention
  ○ Described as palliative care or contain ≥2 domains of palliative care as defined by the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care[5]
• Comparator:
  ○ Usual care, social calls, educational materials, ad hoc palliative care
• Outcomes:
  ○ Healthcare use (hospitalizations and emergency department visits), general and disease-specific quality of life, symptom burden
• Study Design:
  ○ Randomized clinical trials
	• Sample:
	  ○ Individuals <18 years old
	  ○ Co-morbid cancer in ≥50% of enrolled patients
	• Intervention:
	  ○ Palliative care consultation for withdrawal of life-sustaining therapies in the ICU
	  ○ Caregiver is the exclusive or primary target of intervention
	• Study Design:
	  ○ Non-randomized studies

eTable 2.2. Trial Characteristics and Outcomes of 7 Palliative Care Interventions at Low Risk of Bias in Subjective and Objective Outcomes.

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Janssens et al, 2019 (Switzerland)[6]	Parallel	COPD, stage III or IV and/or treatment with either home oxygen or home mechanical ventilation and/or ≥ 1 hospital admissions in the previous year for an acute exacerbation	16.3	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	Home visits by nurses focused on coordination of care, symptoms, nutrition, social and spiritual needs, illness understanding and ACP, and caregiver support. All cases discussed with a palliative care physician.	26	Yes	Usual Care	23	Low	N/A
Possin et al, 2019 (USA)[7]	Parallel	Dementia	12.2	Structure and Process; Physical; Psychological; Social; Ethical and Legal	The Care Ecosystem: telephone- and internet-based supportive care (education, symptoms, legal and financial, safety concerns) delivered by care team navigators and APN, SW, and pharmacist. Monthly telephone calls for 12 months.	512	No	Usual Care	268	Low	Low

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Wong et al, 2016 (Hong Kong)[4]	Parallel	HF with ≥2 of: NYHA class III or IV; ≤ 1-year estimated life expectancy, ≥3 HF-related hospitalizations within 1 year; physical or psychological symptoms despite optimal tolerated therapy	NR	Structure and Process; Physical; Psychological; Social; Spiritual; Care of the Imminently Dying; Ethical and Legal	Transitional care: RN-led case manager, volunteers conducted weekly visits and phone calls for 4 weeks then monthly for 12 weeks. Supported by palliative care MD.	43	Yes	Usual Care: Palliative care clinic consultation, discharge advice on symptom management and medication. Two social placebo calls; ad hoc home-visits.	41	Low	Low
Bekelman et al, 2015 (USA)[8]	Parallel	HF with KCCQ<60	6.9	Structure and Process; Physical; Psychological; Social;	PCDM: RN, primary care MD, cardiologist, psychiatrist; collaborative care HF disease management, screening for and treatment of depression, and daily telemonitoring with patient self-care support.	187	No	Usual Care ± telemonitoring	197	Low	Low

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Higginson et al, 2014 (UK)[9]	Parallel	Mixed: cancer (20%), COPD (54%), HF (5%), interstitial lung disease (18%), and other (3%). and MRC dyspnea scale ≥2	3.8	Structure and Process; Physical; Psychological; Social; Spiritual	Breathlessness Support Service: interprofessional service, respiratory MD, palliative care MD, PT and OT. Two clinic visits and home assessment.	53	Yes	Usual Care	52	Low	Low
Au et al, 2012 (USA)[10]	Cluster, Parallel	COPD: COPD as defined by the GOLD criteria and identify primary COPD MD	NR	Social, Ethical	One-page feedback form addressing goals of care, communication and dying preferences distributed to MDs to increase the self-efficacy of clinicians and patients for discussing end-of-life care.	194	No	Usual Care	182	Low	Low

					Intervention			Control		Risk of Bias	
Study (Country)	Design	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Gade et al, 2008 (Australia)[11]	Parallel	Mixed: hospitalized patients with a life limiting illness ≤ 1-year estimated life expectancy – HF (7.6%), COPD (12.9%), cancer (31.5%), dementia (4.2%), stroke (6.9%), CKD (3.7%)	59	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	IPCS: consultation with palliative care MD, RN, SW and chaplain who assessed and managed symptoms, psychosocial and spiritual support, end-of-life planning, and post-hospital care.	275	Yes	Usual Care	237	Low	Low

HF – Heart failure, COPD – Chronic obstructive pulmonary disease, CAD – coronary artery disease, ESRD – End-stage renal disease, AML – Amyotrophic lateral sclerosis, MD - Physician, RN – Registered nurse, NP – Nurse practitioner, SW – Social work, ACP – Advance care plan, GOLD - Global Initiative for Chronic Obstructive Lung Disease, NYHA – New York Heart Association, KCCQ – Kansas City cardiomyopathy questionnaire , EFFECT - Enhanced Feedback for Effective Cardiac Treatment, ESCAPE - Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness, CASA – Collaborative Care to Alleviate Symptoms and Adjust to Illness, PREFER - Palliative Advanced Home Care and Heart Failure Care, PCDM – Patient-Centred Disease Management, IPCS – interdisciplinary palliative care service, PPS - Palliative Performance scale, NR – Not reported

eTable 2.3. Trial Characteristics and Outcomes of 18 Palliative Care Interventions at High Risk of Bias in Either Subjective or Objective Outcomes.

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Van den Block et al, 2019 (Belgium, England, Finland, Italy, the Netherlands, Poland, and Switzerland)[12]	Cluster, Parallel	Mixed, nursing home (12% cancer)	100	Structure and Process; Physical; Psychological; Social; Spiritual; Care of the Imminently Dying; Ethical and Legal	6-step program implemented over a 12-month period: (1) ACP; (2) review of resident needs and problems; (3) coordination of care via monthly multidisciplinary meetings; (4) symptom management; (5) end-of-life care; and (6) care after death	830	No	Usual Care	704	High	High
Van Spall et al, 2019 (Canada)[13]	Cluster, Parallel	HF, hospitalized with a most responsible diagnosis of HF	9.9	Structure and Process; Physical; Social	Nurse-led self-care education, structured hospital discharge summary, family physician follow-up appointment less than 1 week after discharge, and, for high-risk patients, structured nurse home visits and heart function clinic care	1104	No	Usual Care (transitional care occurred at the discretion of clinicians)	1390	High	Low

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Bekelman et al, 2018 (USA)[14]	Parallel	HF, KCCQ≤70 and 1 symptom (fatigue, shortness of breath, pain, and/or depression)	7.3	Structure and Process; Physical; Psychological; Social; Spiritual	CASA: clinical team (RN, SW, primary care MD, palliative care MD, and cardiologist) reviewed symptoms, psychosocial and provided orders for tests and medications. Twice monthly nurse-led phone calls for symptom assessment and up to 6 SW visits.	158	Yes	Usual Care: Primary care provider or NP provided unstructured symptom and psychosocial assessments; ad hoc visits (3-6 months); ad hoc social work, palliative care, and cardiologist involvement.	159	High	Low
O'Donnell et al, 2018 (USA)[15]	Parallel	HF with NYHA II-IV; currently or recently hospitalized with at ≥1 poor prognostic indicator	38	Structure& and Process; Social; Ethical and Legal	SW-led structured goals of care discussion	26	No	Usual Care with educational materials on palliative care and ACP.	24	High	Low
Agar et al, 2017 (Australia)[16]	Cluster, Parallel	Dementia (FAST ≥6a; Australia–modified Karnofsky Performance Status ≤50)	46	Structure and Process; Social; Ethical and Legal	Facilitated case conferencing: RN-led implementation of palliative care plans, training of RN and direct care staff in person-centred palliative care.	64	No	Usual Care	67	SC	High

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Rogers et al, 2017 (USA)[2]	Parallel	HF-related hospitalization with: acute HF; resting dyspnea plus ≥1 sign of volume overload; previous HF hospitalization within past year; ESCAPE risk score ≥4	28.7	Structure and Process; Physical; Psychological; Social; Spiritual; Care of the Imminently Dying; Ethical and Legal	PAL-HF: Palliative care NP and MD, cardiology team	75	Yes	Usual Care: cardiologist-directed team care with HF expertise, ad hoc palliative care referral.	75	High	Low
Steinhauser et al, 2017 (USA)[17]	Parallel (3-arm)	Mixed: HF (NYHA III-IV), COPD (FEV1 ≤25% or O2-dependent), pulmonary fibrosis (TLC<50%), ESRD (on dialysis), cancer (stage IV solid tumors, stage IIIB NSCLC and pancreatic cancer, recurrent or refractory hematologic malignancy)	4.1	Spiritual, Psychological	SW-led in person interviews (x4) over 1 month focusing on life review, issues of forgiveness, regret, and things left unsaid or undone, and heritage and legacy.	75	No	Usual Care (attention control not included in this systematic review)	72	High	N/A

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Sidebottom et al, 2015 (USA)[18]	Parallel	HF with HF-related hospitalization	8.2	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	Consultation with palliative care MD, nurse specialist, SW, and chaplain; assessed symptoms; emotional, spiritual, and psychosocial; coordination of care; recommendations for future treatment; referrals;	116	Yes	Usual Care	116	High	High
Brännström et al, 2014 (Sweden)[19]	Parallel	HF with NYHA class III−IV and ≥1 of the following: HF-related hospitalization in the preceding 6 months; the need for frequent or continual intravenous medication support; poor quality of life; cardiac cachexia within 6-12 months; estimated life expectancy < 1 year.	16.7	Structure and Process; Physical; Psychological; Social; Spiritual; Care of the Imminently Dying; Ethical and Legal	PREFER: specialized nurses, palliative care nurses, cardiologist, palliative care MD, physiotherapist, and occupational therapist; structured, twice monthly person-centred care meetings at home.	36	Yes	Usual Care: provided mainly by general practitioners or doctors and/or the nurse-led heart failure clinic at the Medicine-Geriatrics department.	36	High	SC

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Radwany et al, 2014 (USA)[20]	Parallel	Mixed (% not reported): cancer, HF (stage C), COPD (on home O2), diabetes with complications, ESRD on dialysis, Cirrhosis, AML with aspiration, Parkinson's disease (stage 3 or 4), pulmonary hypertension	17.5	Structure and Process; Physical; Psychological; Social; Spiritual; Care of the Imminently Dying; Ethical and Legal	Palliative care MD, geriatrician, care manager, nurse specialist, SW, spiritual advisor and pharmacist. 2 home visits for biopsychosocial, spiritual and symptom needs, emergency response plan, education, and completing ACP and legal documents. 24-hour phone availability, monthly phone calls for 1 year.	40	Yes	Usual Care	40	High	SC
Sampson et al, 2011 (UK)[21]	Parallel	Dementia (FAST ≥6d) hospitalized with a treatable acute medical illness	9.1	Physical, Psychological, Social, Spiritual, Ethical and Legal	Nurse-led consultation with input from interprofessional team and up to 4 visits to address illness understanding, symptoms, spiritual, psychological and social supports and advance directives.	22	No	Usual Care	11	High	High

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Pantilat et al, 2010 (USA)[22]	Parallel	Mixed: hospitalized patients with HF (51%), cancer (22%), COPD (20%), cirrhosis (6%)	NR	Structure and Process; Physical; Psychological; Social; Spiritual;	Consultation and daily inpatient visit from palliative care MD who assessed symptoms and psychosocial and spiritual needs and discussed treatment preferences.	54	Yes	Usual Care with education on diet and exercise	53	High	N/A
Farquhar et al, 2016 (UK)[23]	Parallel	Mixed: COPD (83% - 47% severe/very severe), other noncancer illness (17%)	2	Structure and Process; Physical; Psychological; Social;	BIS: PT-led and MD with home and telephone visits over 8 weeks addressed symptoms, psychological, ACP, education and self-management.	44	Yes	Usual Care	43	High	Low

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Aiken et al, 2006 (USA)[24]	Parallel	Mixed: HF (NYAH III-IV – 67.8%) and COPD (O2-dependent – 32.2%) with ≤2 years estimated life expectancy and treatment in an emergency department, urgent care facility, or hospital within 3 months.	NR	Structure and Process; Physical, Social, Spiritual, Psychological, Ethical and Legal	PhoenixCare: RN-led home-based case management (medical director, SW, and pastoral counselor); facilitated care plan (symptoms, psychological, spiritual and financial needs, ACP, and provided educational) to primary care MD, patient/family, and community agencies.	100	No	Usual Care	90	High	High
Rabow et al, 2004 (USA)[25]	Parallel	Mixed: HF (34%), COPD (34%), cancer (35%) with a 1 to 5 year estimated life expectancy and who were not yet ready for hospice care.	NR	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	Comprehensive Care Team: consultation, follow-up and outpatient case management in (SW, MD, RN, chaplain, pharmacist, psychologist, art therapist, volunteer) to address physical, emotional, and spiritual needs.	50	Yes	Usual Care	40	High	High

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Harrison et al, 2002 (Canada)[26]	Parallel	HF: hospitalized patients residing in the regional home care radius expected to be discharged with home nursing care.	10.4	Structure and Process; Social	RN-led support using structured, comprehensive, evidenced-based protocol for self-management and communications between inpatient and outpatient care teams and family to improve the transfer from hospital to home.	92	No	Usual Care	100	High	High
SUPPORT Investigators, 1995 (USA)[27]	Cluster, Parallel	Mixed: hospitalized patients with acute organ system failure (respiratory and multiple organ system failure ± sepsis, chronic disease [HF, COPD or cirrhosis] and cancer	45.6	Structure and Process; Social; Ethical and Legal	RN-led intervention to improve communication by addressing illness understanding about prognosis, addressing goals of care, and facilitating family meetings.	2652	No	Usual Care	2152	High	SC

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Zimmer, et al, 1985 (USA)[28]	Parallel	Mixed: home-bound patients with cancer (19%), stroke (14.6%), rheumatoid arthritis (10.1%), or Other (dementia, CAD, chronic lung disease, multiple sclerosis – 56.4%; each condition less that 10%).	44	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	Home Healthcare Team: MD, NP and SW provided 24/7 telephone support as well as home visits and care during hospitalization. Addressed symptoms, emotional, social and financial needs.	82	Yes	Usual Care	76	High	High

HF – Heart failure, COPD – Chronic obstructive pulmonary disease, CAD – coronary artery disease, ESRD – End-stage renal disease, AML – Amyotrophic lateral sclerosis, MD - Physician, RN – Registered nurse, NP – Nurse practitioner, APN – Advanced practice nurse, SW – Social work, PT – Physiotherapy, OT – Occupational therapy, ACP – Advance care plan, GOLD - Global Initiative for Chronic Obstructive Lung Disease, NYHA – New York Heart Association, KCCQ – Kansas City cardiomyopathy questionnaire , EFFECT - Enhanced Feedback for Effective Cardiac Treatment, ESCAPE - Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness, CASA – Collaborative Care to Alleviate Symptoms and Adjust to Illness, PREFER - Palliative Advanced Home Care and Heart Failure Care, PCDM – Patient-Centred Disease Management, IPCS – interdisciplinary palliative care service, PPS - Palliative Performance scale, NR – Not reported

eTable 2.4. Trial Characteristics and Outcomes of 3 Palliative Care Interventions with Some Concerns Risk of Bias in Either Subjective or Objective Outcomes.

					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Hopp et al, 2016 (USA)[29]	Parallel	Hospitalized patients with HF with ≥1 of: EFFECT score indicating ≥33% 1-year mortality risk; NYHA class III or IV.	23.8	Structure and Process; Physical; Social; Ethical and Legal	Clinical interviews with palliative care MD and RN for symptoms, goals of care, advance care planning, code status, and desired post-treatment residential setting. All had ≥1 palliative care consultation. Ad hoc chaplains and SW.	43	Yes	Usual Care	42	N/A	SC
Brumley et al, 2007 (USA)[30]	Parallel	Mixed: HF (33%), COPD (21%), cancer (47%) with ≤ 1-year estimated life expectancy, ≥1 ED visit or hospitalization within 1 year, and PPS score ≤ 70%.	75	Structure and Process; Physical; Psychological; Social; Spiritual; Ethical and Legal	Palliative care MD, RN and SW provided home-based care to assess and manage physical, medical, psychological, social, and spiritual needs with 24-hour call availability	152	Yes	Usual Care (Medicare guidelines for home healthcare criteria)	145	SC	SC
					Intervention			Control		Risk of Bias	
Study (Country)	**Design**	**Patient Population**	**Died During Study (%)**	**Palliative Care Domains Addressed**	**Description**	**n**	**Presence of Palliative Care Physician**	**Description**	**n**	**Subjective Outcomes**	**Objective Outcomes**
Ahronheim et al, 2000 (USA)[31]	Parallel	Dementia: hospitalized patients with	24	Structure and Process; Physical;	Consultation and daily visits by MD and RN	48	Yes	Usual Care	51	N/A	SC

		advanced dementia (FAST≥6d) with stable neurological deficits for ≥ 1 month		Psychological; Social; Ethical and Legal	to address symptoms, advance directives, goals of care, patient rights, emotional support, discussions surrounding place of death.						

HF – Heart failure, COPD – Chronic obstructive pulmonary disease, CAD – coronary artery disease, ESRD – End-stage renal disease, AML – Amyotrophic lateral sclerosis, MD - Physician, RN – Registered nurse, NP – Nurse practitioner, SW – Social work, ACP – Advance care plan, GOLD - Global Initiative for Chronic Obstructive Lung Disease, NYHA – New York Heart Association, KCCQ – Kansas City cardiomyopathy questionnaire , EFFECT - Enhanced Feedback for Effective Cardiac Treatment, ESCAPE - Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness, CASA – Collaborative Care to Alleviate Symptoms and Adjust to Illness, PREFER - Palliative Advanced Home Care and Heart Failure Care, PCDM – Patient-Centred Disease Management, IPCS – interdisciplinary palliative care service, PPS - Palliative Performance scale, NR – Not reported

eTable 2.5. Risk of Bias Assessments (Subjective Outcomes) of 26 Randomized Clinical Trials of Palliative Care Interventions

Trials with patient-level randomization

First author, year	Randomization	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Summary of Bias[a]
Aiken LS et al., 2006[24]	Low	Low	High	High	SC	High
Bekelman DB et al., 2018[14]	Low	Low	High	High	Low	High
Bekelman DB et al., 2015[8]	Low	Low	Low	High	Low	Low
Brännström M et al., 2014[19]	SC	Low	Low	High	Low	High
Brumley R et al., 2007[30]	Low	Low	SC	High	SC	SC
Farquhar MC et al., 2016[23]	Low	Low	High	High	Low	High
Gade G et al., 2008[11]	Low	Low	Low	High	Low	Low
Harrison MB et al., 2002[26]	Low	Low	High	High	SC	High
Higginson IJ et al., 2014[9]	Low	Low	Low	High	Low	Low
Janssens JP et al., 2019[6]	Low	Low	Low	High	Low	Low
O'Donnell AE et al., 2018[15]	Low	Low	High	High	Low	High
Pantilat SZ et al., 2010[22]	SC	High	High	High	SC	High
Possin KL et al, 2019 [7]	Low	Low	Low	High	Low	Low
Rabow MW et al., 2004[25]	High	High	Low	High	SC	High
Radwany SM et al., 2014[20]	SC	Low	High	High	Low	High
Rogers JG et al., 2017[2]	Low	Low	High	High	Low	High
Sampson EL et al., 2011[21]	Low	High	High	High	SC	High
Sidebottom AC et al., 2015[18]	Low	High	High	High	Low	High
Steinhauser KE et al., 2017[17]	Low	Low	High	High	Low	High
Wong FKY et al., 2016[4]	Low	Low	Low	High	Low	Low
Zimmer JG et al., 1985[28]	High	High	High	High	SC	High

[a]Domain #4 is omitted from summary judgements as all studies are high risk of bias.

RCTs without subjective outcome measures: Ahronheim JC et al., 2000[31], Hopp FP et al., 2016[29]

Trials with cluster-level randomization

First author, year	Randomization	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Summary of Bias[a]
Agar M et al., 2017[16]	Low	Low	SC	High	Low	SC
Au DH et al., 2012[10]	Low	Low	Low	High	Low	Low
SUPPORT Investigators, 1995[27]	Low	Low	High	High	SC	High
Van den Block L et al., 2019[12]	Low	Low	High	High	Low	High
Van Spall HGC et al, 2019[13]	Low	Low	High	High	Low	High

[a]Domain #4 are omitted from summary judgements as all studies are high risk of bias.

eTable 2.6. Risk of Bias Assessments (Objective Outcomes) of 26 Randomized Clinical Trials of Palliative Care Interventions

Trials with patient-level randomization

First author, year	Randomization	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Summary of Bias
Ahronheim JC et al., 2000[31]	SC	Low	Low	Low	SC	SC
Aiken LS et al., 2006[24]	Low	Low	SC	Low	SC	High
Bekelman DB et al., 2018[14]	Low	Low	Low	Low	Low	Low
Bekelman DB et al., 2015[8]	Low	Low	Low	Low	Low	Low
Brännström M et al., 2014[19]	SC	Low	Low	Low	Low	SC
Brumley R et al., 2007[30]	Low	Low	Low	Low	SC	SC
Farquhar MC et al., 2016[23]	Low	Low	Low	Low	Low	Low
Gade G et al., 2008[11]	Low	Low	Low	Low	Low	Low
Harrison MB et al., 2002[26]	Low	Low	SC	Low	SC	High
Higginson IJ et al., 2014[9]	Low	Low	Low	Low	Low	Low
Hopp FP et al., 2016[29]	SC	Low	Low	Low	SC	SC
Janssens JP et al., 2019[6]	Low	Low	Low	Low	Low	Low
O'Donnell AE et al., 2018[15]	Low	Low	Low	Low	Low	Low
Possin KL et al, 2019 [7]	Low	Low	Low	Low	Low	Low

Rabow MW et al., 2004[25]	High	High	Low	Low	SC	High
Radwany SM et al., 2014[20]	SC	Low	Low	Low	Low	SC
Rogers JG et al., 2017[2]	Low	Low	Low	Low	Low	Low
Sampson EL et al., 2011[21]	Low	High	High	Low	SC	High
Sidebottom AC et al., 2015[18]	Low	High	SC	Low	Low	High
Wong FKY et al., 2016[4]	Low	Low	Low	Low	Low	Low
Zimmer JG et al., 1985[28]	High	High	Low	Low	SC	High

RCTs without objective outcome measures: Janssens JP et al., 2019[6], Pantilat SZ et al., 2010[22], Steinhauser KE et al., 2017[17]

Trials with cluster-level randomization

First author, year	Randomization	Deviation from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Summary of Bias
Agar M et al., 2017[16]	Low	Low	High	Low	Low	High
Au DH et al., 2012[10]	Low	Low	Low	Low	Low	Low
SUPPORT Investigators, 1995[27]	Low	Low	High	Low	SC	SC
Van den Block L et al., 2019[12]	Low	Low	High	Low	Low	High
Van Spall HGC et al, 2019[13]	Low	Low	Low	Low	Low	Low

eTable 2.7. Results of Secondary Analyses of Palliative Care Interventions

Outcome Measure	Summary Estimate (95% CI)*	p-value
Emergency Department Use		
Meta-Regression Analyses		
Presence of Palliative Care MD	0.60 (0.38-0.95)	0.03
Heart Failure	0.71(0.43-1.17)	0.18
Mixed Conditions	0.81 (0.53-1.24)	0.34
Dementia	0.92 (0.53-1.58)	0.75
Follow-up Time	1.03 (0.98-1.08)	0.27
Other Secondary Analyses		
Interdisciplinary Care Team	0.87 (0.72-1.06)	--
Home Visits	0.85 (0.66-1.08)	--
Dementia Excluded	0.77 (0.59-1.01)	--
Mixed (Cancer) Excluded	0.82 (0.63-1.07)	--
Hospitalization		
Meta-Regression Analyses		
Presence of Palliative Care MD	0.74 (0.55-1.00)	0.05
Heart Failure	0.83 (0.67-1.03)	0.09
Mixed Conditions	1.02 (0.64-1.63)	0.94
Dementia	1.04 (0.72-1.50)	0.85
Follow-up Time	1.00 (0.96-1.03)	0.77
Other Secondary Analyses		
Interdisciplinary Care Team	0.93 (0.78-1.11)	--
Home Visits	0.77 (0.53-1.12)	--
Dementia Excluded	0.88 (0.74-1.05)	--
Mixed (Cancer) Excluded	0.90 (0.76-1.06)	--
Disease-Generic QOL		
Meta-Regression Analyses		
Presence of Palliative Care MD	0.35 (0.13-0.57)	<0.001
Heart Failure	0.17 (-0.23-0.56)	0.40
Mixed Conditions	0.19 (-0.69-1.06)	0.67
Dementia	--	--
Follow-up Time	-0.07 (-0.21-0.08)	0.38
Other Secondary Analyses		
Interdisciplinary Care Team	0.18 (-0.29-0.64)	--
Home Visits	0.15 (-0.40-0.70)	--
Dementia Excluded	0.18 (-0.24-0.61)	--
Mixed (Cancer) Excluded	0.19 (-0.31-0.69)	--

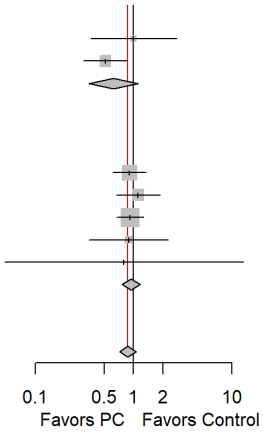
Outcome Measure	Summary Estimate (95% CI)*	p-value
Disease-Specific QOL		
Meta-Regression Analyses		
Presence of Palliative Care MD	0.18 (-0.01-0.37)	0.06
Heart Failure	0.05 (-0.21-0.30)	0.73
Mixed Conditions	0.18 (-0.31-0.67)	0.47
Dementia	0.07 (-0.56-0.70)	0.83
Follow-up Time	-0.01 (-0.07-0.05)	0.75
Other Secondary Analyses		
Interdisciplinary Care Team	0.15 (0.02-0.29)	--
Home Visits	0.37 (0.05-0.69)	--
Dementia Excluded	0.13 (0.01-0.25)	--
Mixed (Cancer) Excluded	0.12 (0.00-0.23)	--
Symptoms		
Meta-Regression Analyses		
Presence of Palliative Care MD	-0.16 (-0.27--0.06)	0.002
Heart Failure	-0.16 (-0.32--0.01)	0.04
Mixed Conditions	-0.10 (-0.21-0.00)	0.05
Dementia	-0.20 (-1.43-1.03)	0.75
Follow-up Time	0.01 (0.00-0.02)	0.09
Other Secondary Analyses		
Interdisciplinary Care Team	-0.11 (-0.19--0.02)	--
Home Visits	-0.15 (-0.34-0.03)	--
Dementia Excluded	-0.12 (-0.20--0.03)	--
Mixed (Cancer) Excluded	-0.16 (-0.31--0.01)	--
Advance Care Planning		
Meta-Regression Analyses		
Presence of Palliative Care MD	3.98 (1.73-9.17)	0.001
Heart Failure	4.53 (1.16-17.71)	0.03
Mixed Conditions	1.72 (0.83-3.57)	0.20
Dementia	7.28 (1.16-45.81)	0.03
COPD	3.40 (1.33-8.68)	0.01
Follow-up Time	--	--
Other Secondary Analyses		
Interdisciplinary Care Team	3.34 (2.10-5.29)	--
Home Visits	--	--
Dementia Excluded	2.65 (1.35-5.21)	--
Mixed (Cancer) Excluded	3.74 (2.39-5.83)	--

*All summary estimates are presented as OR (95% CIs) except for meta-regression analyses of measures of Quality of Life and Symptoms, which are presented as beta-estimates.
COPD – Chronic Obstructive Pulmonary Disease

eFigure 2.1. Secondary Analysis of the Association Between Palliative Care and Healthcare Use for (A) Emergency department use with interdisciplinary teams involving a physician, (B) Emergency department use with home visits, (C) Emergency department use with trials of dementia excluded, (D) Emergency department use with trials of mixed disease excluded, (E) Hospitalization with interdisciplinary teams involving a physician, (F) Hospitalization with home visits, (G) Hospitalization with trials of dementia excluded, (H) Hospitalization with trials of mixed disease excluded . Data are presented as the odds and 95% CIs (error bars) of at least one ED visit or hospitalization during study follow-up. The shaded squares are proportionally sized to reflect study weight and the shaded diamonds represent pooled odds and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns) HF – heart failure.

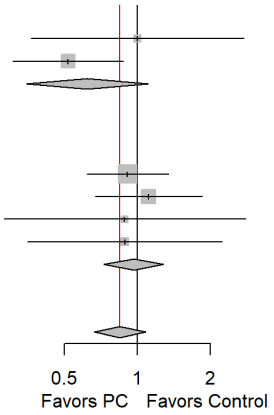
A

Study	Palliative care E/N	CR	Control E/N	CR	Disease	OR [95% CI]	Weight
Some Concerns							
Radwany, 2014	10/40	0.25	10/40	0.25	Mixed	1.00 [0.36; 2.75]	3.7%
Brumley, 2007	31/152	0.20	48/145	0.33	Mixed	0.52 [0.31; 0.87]	13.7%
Random effects model						0.62 [0.35; 1.10]	17.4%
Heterogeneity: I^2 = 22%, τ^2 = 0.0475, p = 0.26							
High							
Van Spall, 2019	56/248	0.23	81/334	0.24	HF	0.91 [0.62; 1.34]	25.0%
Van den Block, 2019	33/206	0.16	37/253	0.15	Mixed	1.11 [0.67; 1.85]	14.5%
Possin, 2019	199/452	0.44	110/239	0.46	Dementia	0.92 [0.67; 1.26]	38.1%
Aiken, 2006	10/100	0.10	10/90	0.11	Mixed	0.89 [0.35; 2.25]	4.4%
Rabow, 2004	1/50	0.02	1/40	0.02	Mixed	0.80 [0.05; 13.13]	0.5%
Random effects model						0.95 [0.76; 1.17]	82.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.97							
Random effects model						**0.87 [0.72; 1.06]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.55							
Residual heterogeneity: I^2 = 0%, p = 0.88							

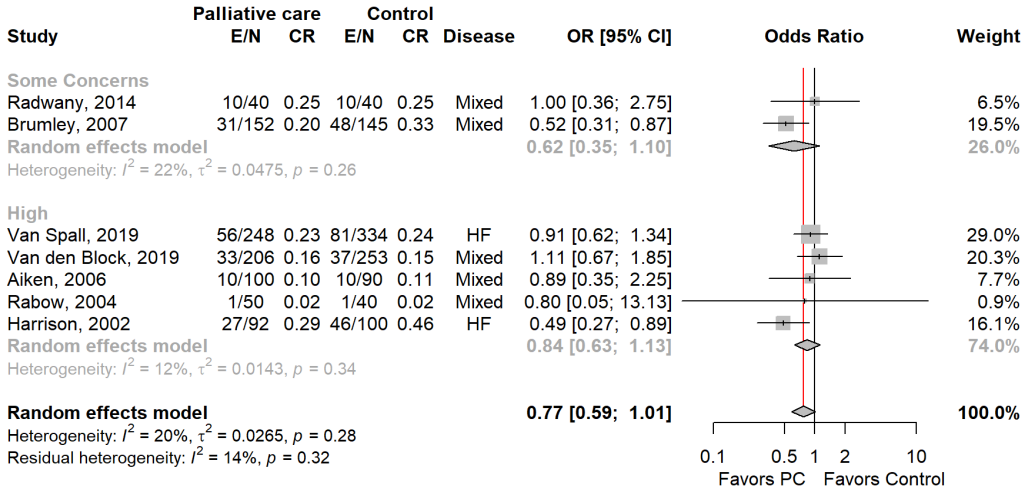


B

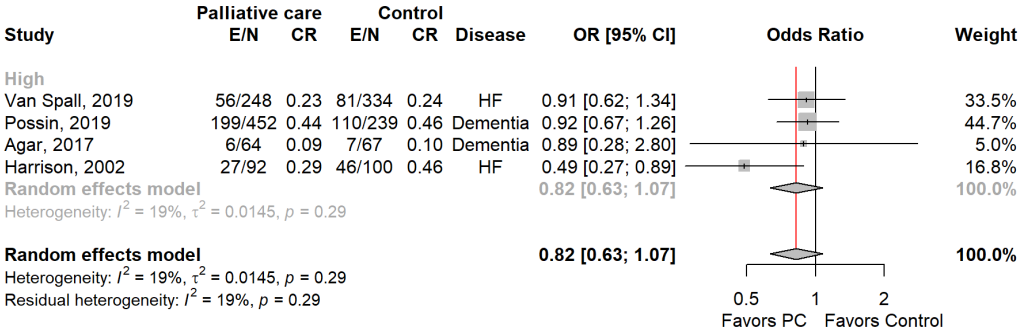
Study	Palliative care E/N	CR	Control E/N	CR	Disease	OR [95% CI]	Weight
Some Concerns							
Radwany, 2014	10/40	0.25	10/40	0.25	Mixed	1.00 [0.36; 2.75]	5.7%
Brumley, 2007	31/152	0.20	48/145	0.33	Mixed	0.52 [0.31; 0.87]	21.4%
Random effects model						0.62 [0.35; 1.10]	27.1%
Heterogeneity: I^2 = 22%, τ^2 = 0.0475, p = 0.26							
High							
Van Spall, 2019	56/248	0.23	81/334	0.24	HF	0.91 [0.62; 1.34]	38.9%
Van den Block, 2019	33/206	0.16	37/253	0.15	Mixed	1.11 [0.67; 1.85]	22.6%
Agar, 2017	6/64	0.09	7/67	0.10	Dementia	0.89 [0.28; 2.80]	4.5%
Aiken, 2006	10/100	0.10	10/90	0.11	Mixed	0.89 [0.35; 2.25]	6.9%
Random effects model						0.97 [0.73; 1.28]	72.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.93							
Random effects model						**0.85 [0.66; 1.08]**	**100.0%**
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.45							
Residual heterogeneity: I^2 = 0%, p = 0.79							



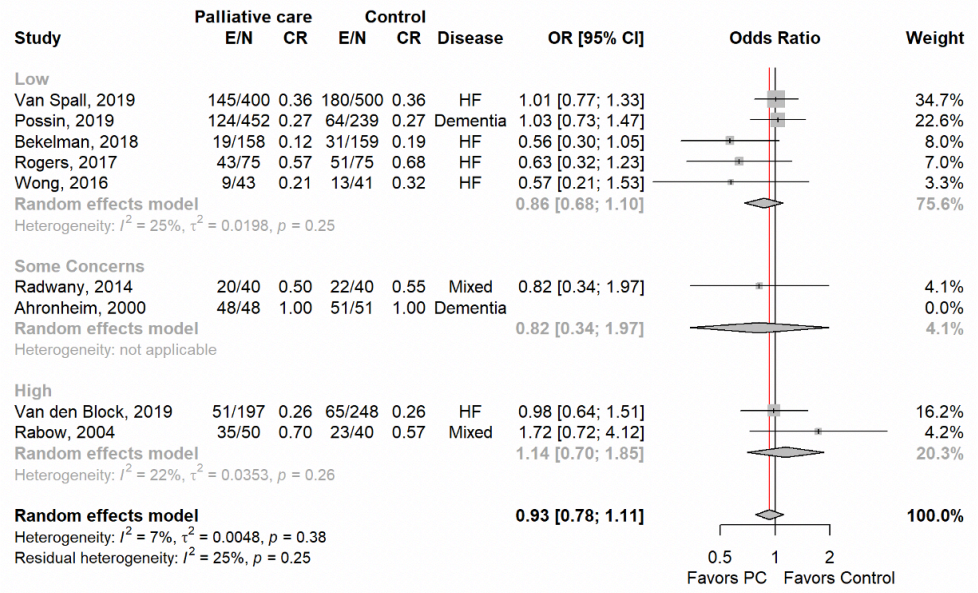
C


Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Some Concerns
Radwany, 2014 10/40 0.25 10/40 0.25 Mixed 1.00 [0.36; 2.75] 6.5%
Brumley, 2007 31/152 0.20 48/145 0.33 Mixed 0.52 [0.31; 0.87] 19.5%
Random effects model 0.62 [0.35; 1.10] 26.0%
Heterogeneity: I^2 = 22%, τ^2 = 0.0475, p = 0.26
High
Van Spall, 2019 56/248 0.23 81/334 0.24 HF 0.91 [0.62; 1.34] 29.0%
Van den Block, 2019 33/206 0.16 37/253 0.15 Mixed 1.11 [0.67; 1.85] 20.3%
Aiken, 2006 10/100 0.10 10/90 0.11 Mixed 0.89 [0.35; 2.25] 7.7%
Rabow, 2004 1/50 0.02 1/40 0.02 Mixed 0.80 [0.05; 13.13] 0.9%
Harrison, 2002 27/92 0.29 46/100 0.46 HF 0.49 [0.27; 0.89] 16.1%
Random effects model 0.84 [0.63; 1.13] 74.0%
Heterogeneity: I^2 = 12%, τ^2 = 0.0143, p = 0.34
Random effects model 0.77 [0.59; 1.01] 100.0%
Heterogeneity: I^2 = 20%, τ^2 = 0.0265, p = 0.28
Residual heterogeneity: I^2 = 14%, p = 0.32
0.1 0.5 1 2 10
Favors PC Favors Control

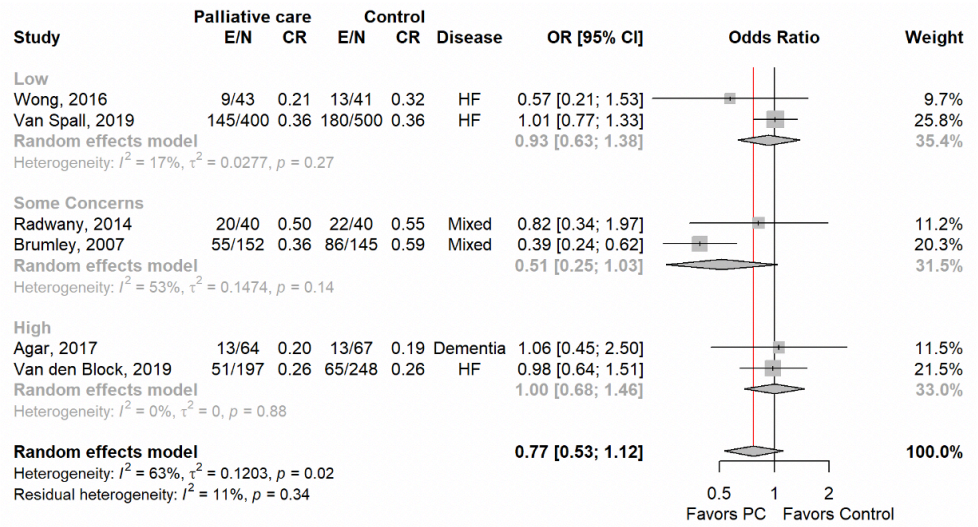
D


Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
High
Van Spall, 2019 56/248 0.23 81/334 0.24 HF 0.91 [0.62; 1.34] 33.5%
Possin, 2019 199/452 0.44 110/239 0.46 Dementia 0.92 [0.67; 1.26] 44.7%
Agar, 2017 6/64 0.09 7/67 0.10 Dementia 0.89 [0.28; 2.80] 5.0%
Harrison, 2002 27/92 0.29 46/100 0.46 HF 0.49 [0.27; 0.89] 16.8%
Random effects model 0.82 [0.63; 1.07] 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.0145, p = 0.29
Random effects model 0.82 [0.63; 1.07] 100.0%
Heterogeneity: I^2 = 19%, τ^2 = 0.0145, p = 0.29
Residual heterogeneity: I^2 = 19%, p = 0.29
0.5 1 2
Favors PC Favors Control

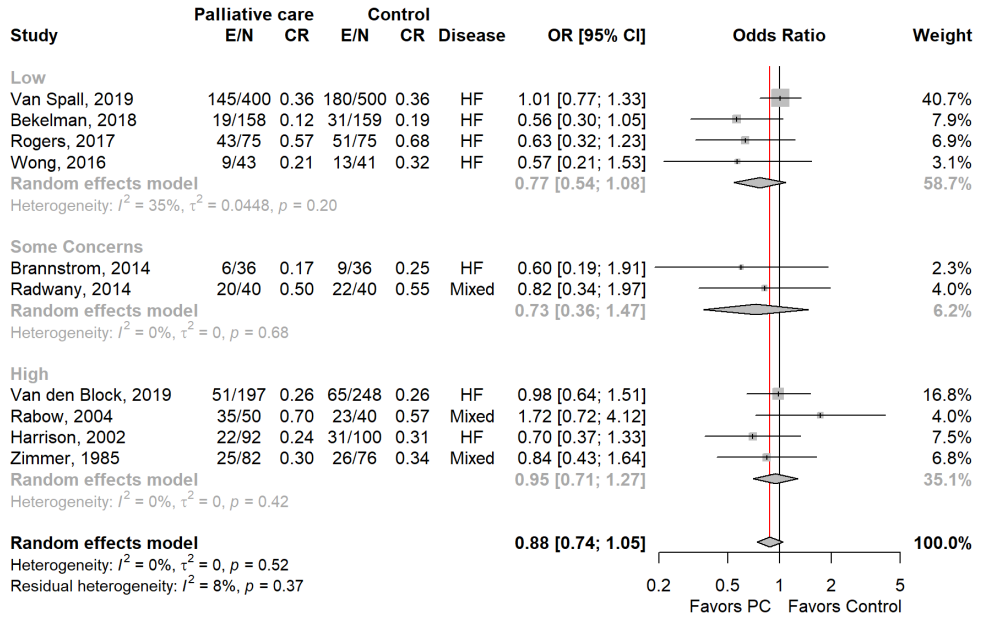
E


Palliative care
Control
Study
E/N CR E/N CR Disease OR [95% CI] Odds Ratio Weight
Low
Van Spall, 2019 145/400 0.36 180/500 0.36 HF 1.01 [0.77; 1.33] 34.7%
Possin, 2019 124/452 0.27 64/239 0.27 Dementia 1.03 [0.73; 1.47] 22.6%
Bekelman, 2018 19/158 0.12 31/159 0.19 HF 0.56 [0.30; 1.05] 8.0%
Rogers, 2017 43/75 0.57 51/75 0.68 HF 0.63 [0.32; 1.23] 7.0%
Wong, 2016 9/43 0.21 13/41 0.32 HF 0.57 [0.21; 1.53] 3.3%
Random effects model 0.86 [0.68; 1.10] 75.6%
Heterogeneity: I^2 = 25%, τ^2 = 0.0198, p = 0.25
Some Concerns
Radwany, 2014 20/40 0.50 22/40 0.55 Mixed 0.82 [0.34; 1.97] 4.1%
Ahronheim, 2000 48/48 1.00 51/51 1.00 Dementia 0.0%
Random effects model 0.82 [0.34; 1.97] 4.1%
Heterogeneity: not applicable
High
Van den Block, 2019 51/197 0.26 65/248 0.26 HF 0.98 [0.64; 1.51] 16.2%
Rabow, 2004 35/50 0.70 23/40 0.57 Mixed 1.72 [0.72; 4.12] 4.2%
Random effects model 1.14 [0.70; 1.85] 20.3%
Heterogeneity: I^2 = 22%, τ^2 = 0.0353, p = 0.26
Random effects model 0.93 [0.78; 1.11] 100.0%
Heterogeneity: I^2 = 7%, τ^2 = 0.0048, p = 0.38
Residual heterogeneity: I^2 = 25%, p = 0.25
0.5
1
2
Favors PC
Favors Control

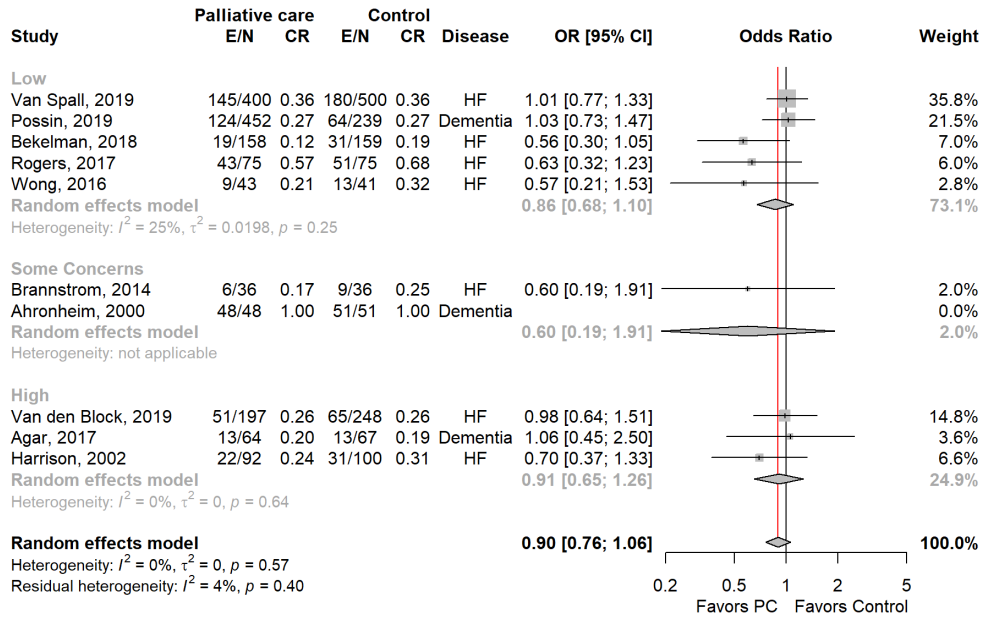
F


Palliative care
Control
Study
E/N CR E/N CR Disease OR [95% CI] Odds Ratio Weight
Low
Wong, 2016 9/43 0.21 13/41 0.32 HF 0.57 [0.21; 1.53] 9.7%
Van Spall, 2019 145/400 0.36 180/500 0.36 HF 1.01 [0.77; 1.33] 25.8%
Random effects model 0.93 [0.63; 1.38] 35.4%
Heterogeneity: I^2 = 17%, τ^2 = 0.0277, p = 0.27
Some Concerns
Radwany, 2014 20/40 0.50 22/40 0.55 Mixed 0.82 [0.34; 1.97] 11.2%
Brumley, 2007 55/152 0.36 86/145 0.59 Mixed 0.39 [0.24; 0.62] 20.3%
Random effects model 0.51 [0.25; 1.03] 31.5%
Heterogeneity: I^2 = 53%, τ^2 = 0.1474, p = 0.14
High
Agar, 2017 13/64 0.20 13/67 0.19 Dementia 1.06 [0.45; 2.50] 11.5%
Van den Block, 2019 51/197 0.26 65/248 0.26 HF 0.98 [0.64; 1.51] 21.5%
Random effects model 1.00 [0.68; 1.46] 33.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.88
Random effects model 0.77 [0.53; 1.12] 100.0%
Heterogeneity: I^2 = 63%, τ^2 = 0.1203, p = 0.02
Residual heterogeneity: I^2 = 11%, p = 0.34
0.5
1
2
Favors PC
Favors Control

G

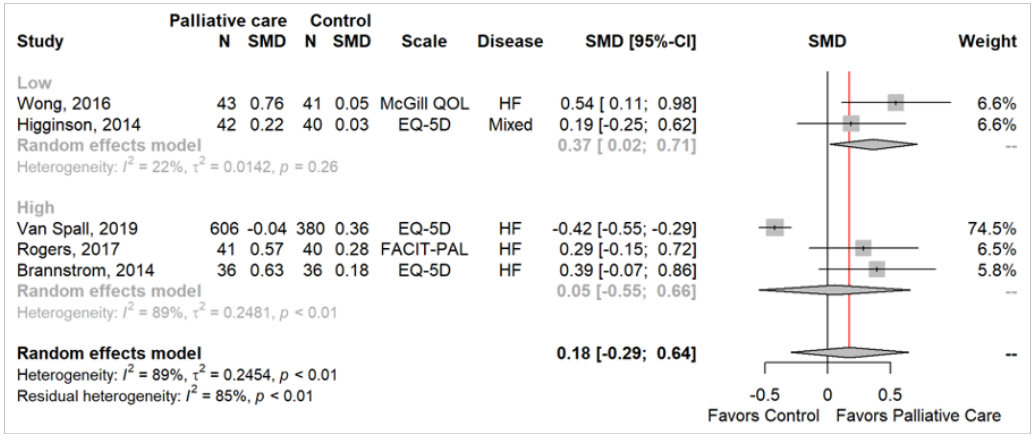

Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Low
Van Spall, 2019 145/400 0.36 180/500 0.36 HF 1.01 [0.77; 1.33] 40.7%
Bekelman, 2018 19/158 0.12 31/159 0.19 HF 0.56 [0.30; 1.05] 7.9%
Rogers, 2017 43/75 0.57 51/75 0.68 HF 0.63 [0.32; 1.23] 6.9%
Wong, 2016 9/43 0.21 13/41 0.32 HF 0.57 [0.21; 1.53] 3.1%
Random effects model 0.77 [0.54; 1.08] 58.7%
Heterogeneity: I^2 = 35%, τ^2 = 0.0448, p = 0.20
Some Concerns
Brannstrom, 2014 6/36 0.17 9/36 0.25 HF 0.60 [0.19; 1.91] 2.3%
Radwany, 2014 20/40 0.50 22/40 0.55 Mixed 0.82 [0.34; 1.97] 4.0%
Random effects model 0.73 [0.36; 1.47] 6.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.68
High
Van den Block, 2019 51/197 0.26 65/248 0.26 HF 0.98 [0.64; 1.51] 16.8%
Rabow, 2004 35/50 0.70 23/40 0.57 Mixed 1.72 [0.72; 4.12] 4.0%
Harrison, 2002 22/92 0.24 31/100 0.31 HF 0.70 [0.37; 1.33] 7.5%
Zimmer, 1985 25/82 0.30 26/76 0.34 Mixed 0.84 [0.43; 1.64] 6.8%
Random effects model 0.95 [0.71; 1.27] 35.1%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42
Random effects model 0.88 [0.74; 1.05] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52
Residual heterogeneity: I^2 = 8%, p = 0.37
0.2 0.5 1 2 5
Favors PC Favors Control

H

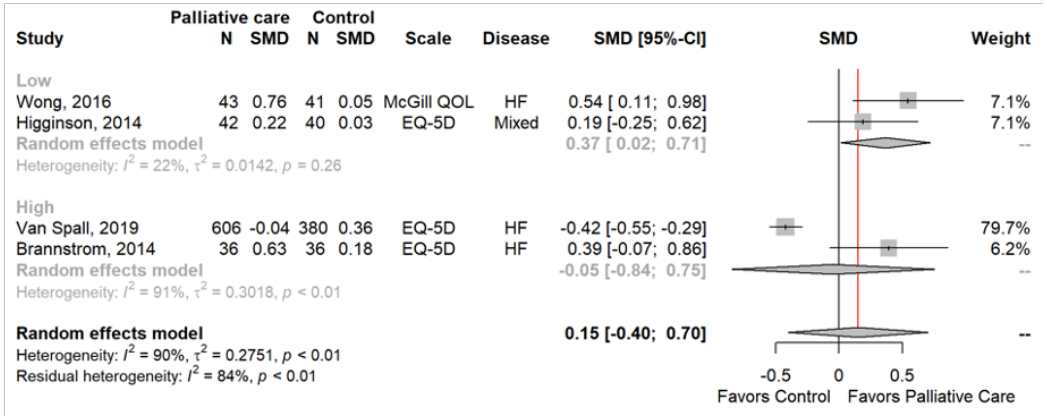

Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Low
Van Spall, 2019 145/400 0.36 180/500 0.36 HF 1.01 [0.77; 1.33] 35.8%
Possin, 2019 124/452 0.27 64/239 0.27 Dementia 1.03 [0.73; 1.47] 21.5%
Bekelman, 2018 19/158 0.12 31/159 0.19 HF 0.56 [0.30; 1.05] 7.0%
Rogers, 2017 43/75 0.57 51/75 0.68 HF 0.63 [0.32; 1.23] 6.0%
Wong, 2016 9/43 0.21 13/41 0.32 HF 0.57 [0.21; 1.53] 2.8%
Random effects model 0.86 [0.68; 1.10] 73.1%
Heterogeneity: I^2 = 25%, τ^2 = 0.0198, p = 0.25
Some Concerns
Brannstrom, 2014 6/36 0.17 9/36 0.25 HF 0.60 [0.19; 1.91] 2.0%
Ahronheim, 2000 48/48 1.00 51/51 1.00 Dementia 0.0%
Random effects model 0.60 [0.19; 1.91] 2.0%
Heterogeneity: not applicable
High
Van den Block, 2019 51/197 0.26 65/248 0.26 HF 0.98 [0.64; 1.51] 14.8%
Agar, 2017 13/64 0.20 13/67 0.19 Dementia 1.06 [0.45; 2.50] 3.6%
Harrison, 2002 22/92 0.24 31/100 0.31 HF 0.70 [0.37; 1.33] 6.6%
Random effects model 0.91 [0.65; 1.26] 24.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64
Random effects model 0.90 [0.76; 1.06] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.57
Residual heterogeneity: I^2 = 4%, p = 0.40
0.2 0.5 1 2 5
Favors PC Favors Control

eFigure 2.2. Secondary Analysis of the Association Between Palliative Care and Quality of Life for (A) Disease-generic QOL with interdisciplinary teams involving a physician, (B) Disease-generic QOL with home visits, (C) Disease-generic QOL with trials of dementia excluded, (D) Disease-generic QOL with trials of mixed disease excluded, (E) Disease-specific QOL with interdisciplinary teams involving a physician, (F) Disease-specific QOL with home visits, (G) Disease-specific QOL with trials of dementia excluded, (H) Disease-specific QOL with trials of mixed disease excluded. Data are presented as the means and 95% CIs (error bars) of the change in quality of life measures from baseline to the end of study follow-up. The shaded squares are proportionally sized to reflect study weight and the shaded diamonds represent pooled standardized mean difference and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). HF – heart failure; EQ-5D – EuroQol-5D; FACIT - Functional Assessment of Chronic Illness Therapy scale.

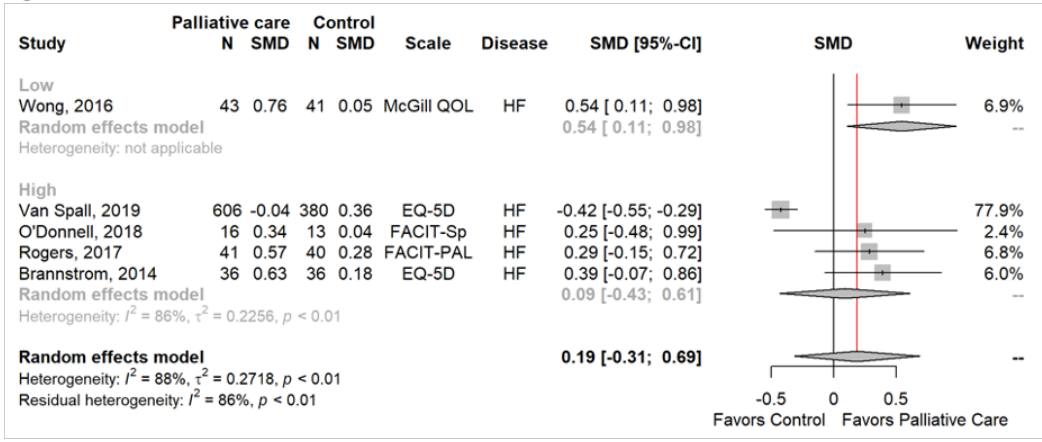
A


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Wong, 2016 43 0.76 41 0.05 McGill QOL HF 0.54 [0.11; 0.98] 6.6%
Higginson, 2014 42 0.22 40 0.03 EQ-5D Mixed 0.19 [-0.25; 0.62] 6.6%
Random effects model 0.37 [0.02; 0.71] --
Heterogeneity: I^2 = 22%, τ^2 = 0.0142, p = 0.26
High
Van Spall, 2019 606 -0.04 380 0.36 EQ-5D HF -0.42 [-0.55; -0.29] 74.5%
Rogers, 2017 41 0.57 40 0.28 FACIT-PAL HF 0.29 [-0.15; 0.72] 6.5%
Brannstrom, 2014 36 0.63 36 0.18 EQ-5D HF 0.39 [-0.07; 0.86] 5.8%
Random effects model 0.05 [-0.55; 0.66] --
Heterogeneity: I^2 = 89%, τ^2 = 0.2481, p < 0.01
Random effects model 0.18 [-0.29; 0.64] --
Heterogeneity: I^2 = 89%, τ^2 = 0.2454, p < 0.01
Residual heterogeneity: I^2 = 85%, p < 0.01
-0.5
0
0.5
Favors Control
Favors Palliative Care

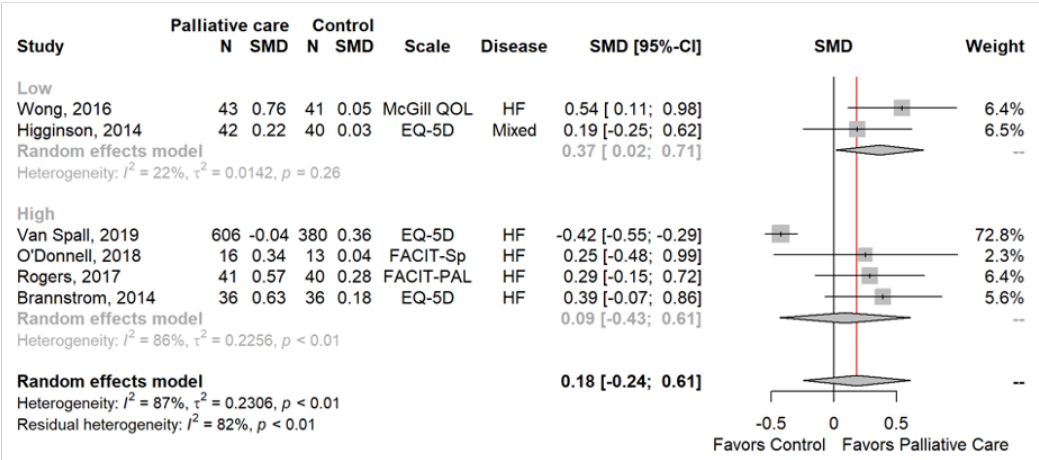
B


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Wong, 2016 43 0.76 41 0.05 McGill QOL HF 0.54 [0.11; 0.98] 7.1%
Higginson, 2014 42 0.22 40 0.03 EQ-5D Mixed 0.19 [-0.25; 0.62] 7.1%
Random effects model 0.37 [0.02; 0.71] --
Heterogeneity: I^2 = 22%, τ^2 = 0.0142, p = 0.26
High
Van Spall, 2019 606 -0.04 380 0.36 EQ-5D HF -0.42 [-0.55; -0.29] 79.7%
Brannstrom, 2014 36 0.63 36 0.18 EQ-5D HF 0.39 [-0.07; 0.86] 6.2%
Random effects model -0.05 [-0.84; 0.75] --
Heterogeneity: I^2 = 91%, τ^2 = 0.3018, p < 0.01
Random effects model 0.15 [-0.40; 0.70] --
Heterogeneity: I^2 = 90%, τ^2 = 0.2751, p < 0.01
Residual heterogeneity: I^2 = 84%, p < 0.01
-0.5
0
0.5
Favors Control
Favors Palliative Care

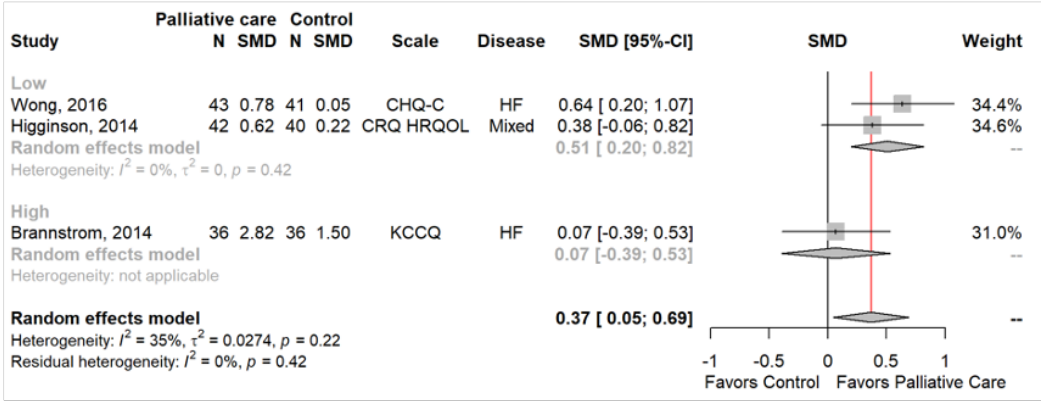
C


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Wong, 2016 43 0.76 41 0.05 McGill QOL HF 0.54 [0.11; 0.98] 6.9%
Random effects model 0.54 [0.11; 0.98] --
Heterogeneity: not applicable
High
Van Spall, 2019 606 -0.04 380 0.36 EQ-5D HF -0.42 [-0.55; -0.29] 77.9%
O'Donnell, 2018 16 0.34 13 0.04 FACIT-Sp HF 0.25 [-0.48; 0.99] 2.4%
Rogers, 2017 41 0.57 40 0.28 FACIT-PAL HF 0.29 [-0.15; 0.72] 6.8%
Brannstrom, 2014 36 0.63 36 0.18 EQ-5D HF 0.39 [-0.07; 0.86] 6.0%
Random effects model 0.09 [-0.43; 0.61] --
Heterogeneity: I^2 = 86%, τ^2 = 0.2256, p < 0.01
Random effects model 0.19 [-0.31; 0.69] --
Heterogeneity: I^2 = 88%, τ^2 = 0.2718, p < 0.01
Residual heterogeneity: I^2 = 86%, p < 0.01
-0.5 0 0.5
Favors Control Favors Palliative Care

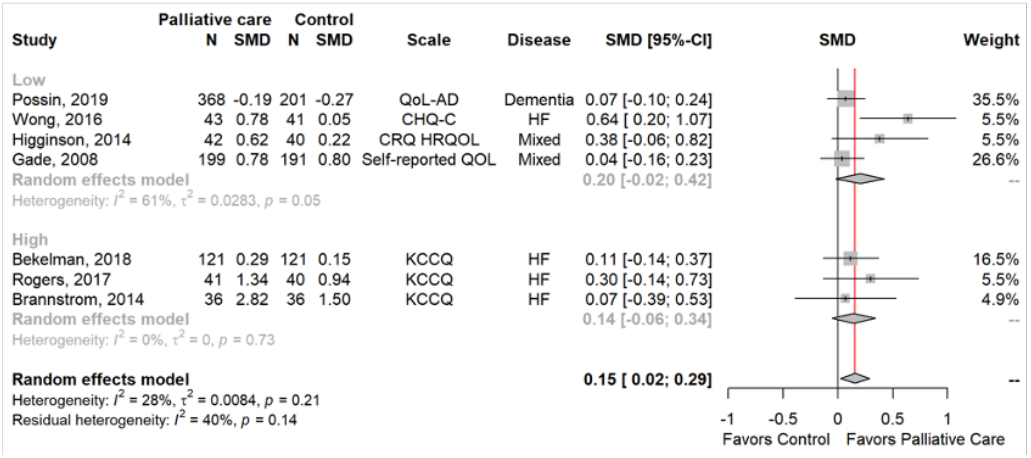
D


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Wong, 2016 43 0.76 41 0.05 McGill QOL HF 0.54 [0.11; 0.98] 6.4%
Higginson, 2014 42 0.22 40 0.03 EQ-5D Mixed 0.19 [-0.25; 0.62] 6.5%
Random effects model 0.37 [0.02; 0.71] --
Heterogeneity: I^2 = 22%, τ^2 = 0.0142, p = 0.26
High
Van Spall, 2019 606 -0.04 380 0.36 EQ-5D HF -0.42 [-0.55; -0.29] 72.8%
O'Donnell, 2018 16 0.34 13 0.04 FACIT-Sp HF 0.25 [-0.48; 0.99] 2.3%
Rogers, 2017 41 0.57 40 0.28 FACIT-PAL HF 0.29 [-0.15; 0.72] 6.4%
Brannstrom, 2014 36 0.63 36 0.18 EQ-5D HF 0.39 [-0.07; 0.86] 5.6%
Random effects model 0.09 [-0.43; 0.61] --
Heterogeneity: I^2 = 86%, τ^2 = 0.2256, p < 0.01
Random effects model 0.18 [-0.24; 0.61] --
Heterogeneity: I^2 = 87%, τ^2 = 0.2306, p < 0.01
Residual heterogeneity: I^2 = 82%, p < 0.01
-0.5 0 0.5
Favors Control Favors Palliative Care

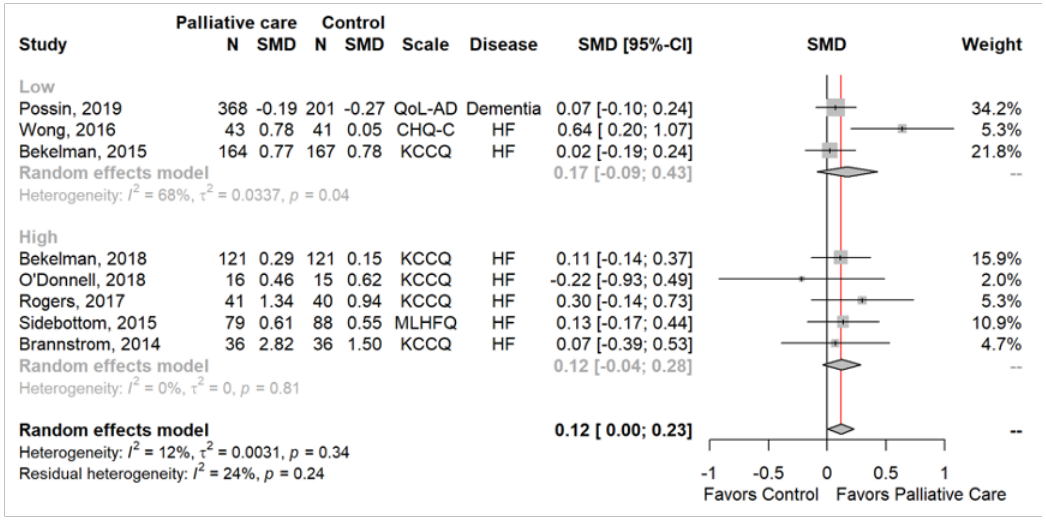
E


Palliative care
Control
Study
N SMD N SMD
Scale
Disease
SMD [95%-CI]
SMD
Weight
Low
Wong, 2016 43 0.78 41 0.05 CHQ-C HF 0.64 [0.20; 1.07] 34.4%
Higginson, 2014 42 0.62 40 0.22 CRQ HRQOL Mixed 0.38 [-0.06; 0.82] 34.6%
Random effects model 0.51 [0.20; 0.82] --
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.42
High
Brannstrom, 2014 36 2.82 36 1.50 KCCQ HF 0.07 [-0.39; 0.53] 31.0%
Random effects model 0.07 [-0.39; 0.53] --
Heterogeneity: not applicable
Random effects model 0.37 [0.05; 0.69] --
Heterogeneity: I^2 = 35%, τ^2 = 0.0274, p = 0.22
Residual heterogeneity: I^2 = 0%, p = 0.42
-1 -0.5 0 0.5 1
Favors Control
Favors Palliative Care

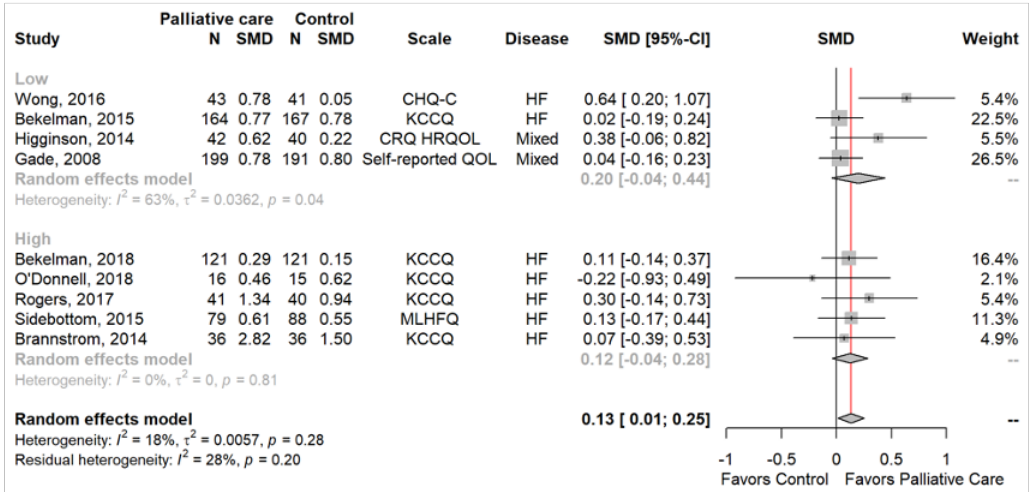
F


Palliative care
Control
Study
N SMD N SMD
Scale
Disease
SMD [95%-CI]
SMD
Weight
Low
Possin, 2019 368 -0.19 201 -0.27 QoL-AD Dementia 0.07 [-0.10; 0.24] 35.5%
Wong, 2016 43 0.78 41 0.05 CHQ-C HF 0.64 [0.20; 1.07] 5.5%
Higginson, 2014 42 0.62 40 0.22 CRQ HRQOL Mixed 0.38 [-0.06; 0.82] 5.5%
Gade, 2008 199 0.78 191 0.80 Self-reported QOL Mixed 0.04 [-0.16; 0.23] 26.6%
Random effects model 0.20 [-0.02; 0.42] --
Heterogeneity: I^2 = 61%, τ^2 = 0.0283, p = 0.05
High
Bekelman, 2018 121 0.29 121 0.15 KCCQ HF 0.11 [-0.14; 0.37] 16.5%
Rogers, 2017 41 1.34 40 0.94 KCCQ HF 0.30 [-0.14; 0.73] 5.5%
Brannstrom, 2014 36 2.82 36 1.50 KCCQ HF 0.07 [-0.39; 0.53] 4.9%
Random effects model 0.14 [-0.06; 0.34] --
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73
Random effects model 0.15 [0.02; 0.29] --
Heterogeneity: I^2 = 28%, τ^2 = 0.0084, p = 0.21
Residual heterogeneity: I^2 = 40%, p = 0.14
-1 -0.5 0 0.5 1
Favors Control
Favors Palliative Care

G


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Possin, 2019 368 -0.19 201 -0.27 QoL-AD Dementia 0.07 [-0.10; 0.24] 34.2%
Wong, 2016 43 0.78 41 0.05 CHQ-C HF 0.64 [0.20; 1.07] 5.3%
Bekelman, 2015 164 0.77 167 0.78 KCCQ HF 0.02 [-0.19; 0.24] 21.8%
Random effects model 0.17 [-0.09; 0.43] --
Heterogeneity: I^2 = 68%, τ^2 = 0.0337, p = 0.04
High
Bekelman, 2018 121 0.29 121 0.15 KCCQ HF 0.11 [-0.14; 0.37] 15.9%
O'Donnell, 2018 16 0.46 15 0.62 KCCQ HF -0.22 [-0.93; 0.49] 2.0%
Rogers, 2017 41 1.34 40 0.94 KCCQ HF 0.30 [-0.14; 0.73] 5.3%
Sidebottom, 2015 79 0.61 88 0.55 MLHFQ HF 0.13 [-0.17; 0.44] 10.9%
Brannstrom, 2014 36 2.82 36 1.50 KCCQ HF 0.07 [-0.39; 0.53] 4.7%
Random effects model 0.12 [-0.04; 0.28] --
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81
Random effects model 0.12 [0.00; 0.23] --
Heterogeneity: I^2 = 12%, τ^2 = 0.0031, p = 0.34
Residual heterogeneity: I^2 = 24%, p = 0.24
-1 -0.5 0 0.5 1
Favors Control Favors Palliative Care

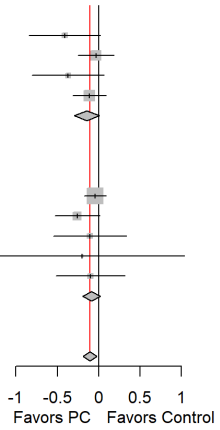
H


Palliative care
Control
Study N SMD N SMD Scale Disease SMD [95%-CI] SMD Weight
Low
Wong, 2016 43 0.78 41 0.05 CHQ-C HF 0.64 [0.20; 1.07] 5.4%
Bekelman, 2015 164 0.77 167 0.78 KCCQ HF 0.02 [-0.19; 0.24] 22.5%
Higginson, 2014 42 0.62 40 0.22 CRQ HRQOL Mixed 0.38 [-0.06; 0.82] 5.5%
Gade, 2008 199 0.78 191 0.80 Self-reported QOL Mixed 0.04 [-0.16; 0.23] 26.5%
Random effects model 0.20 [-0.04; 0.44] --
Heterogeneity: I^2 = 63%, τ^2 = 0.0362, p = 0.04
High
Bekelman, 2018 121 0.29 121 0.15 KCCQ HF 0.11 [-0.14; 0.37] 16.4%
O'Donnell, 2018 16 0.46 15 0.62 KCCQ HF -0.22 [-0.93; 0.49] 2.1%
Rogers, 2017 41 1.34 40 0.94 KCCQ HF 0.30 [-0.14; 0.73] 5.4%
Sidebottom, 2015 79 0.61 88 0.55 MLHFQ HF 0.13 [-0.17; 0.44] 11.3%
Brannstrom, 2014 36 2.82 36 1.50 KCCQ HF 0.07 [-0.39; 0.53] 4.9%
Random effects model 0.12 [-0.04; 0.28] --
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81
Random effects model 0.13 [0.01; 0.25] --
Heterogeneity: I^2 = 18%, τ^2 = 0.0057, p = 0.28
Residual heterogeneity: I^2 = 28%, p = 0.20
-1 -0.5 0 0.5 1
Favors Control Favors Palliative Care

eFigure 2.3. Subgroup Analysis of the Association Between Palliative Care and Symptoms for (A) Interdisciplinary teams involving a physician, (B) Home visits, (C) Trials of dementia excluded, (D) Trials of mixed disease excluded. Data are presented as the means and 95% CIs (error bars) of the change in symptom measures from baseline to the end of study follow-up. The shaded squares are proportionally sized to reflect study weight and the shaded diamonds represent pooled standardized mean difference and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). HF – heart failure; PHQ – Patient Health Questionaire; HADS - Hospital Anxiety and Depression Scale; VAS – Visual Analogue Scale; ESAS – Edmonton Symptom Assessment Scale; MCOHPQ - Modified City of Hope Patient Questionnaire.

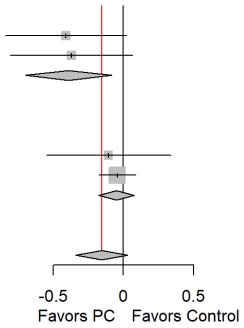
A

Study	Palliative care N	Palliative care SMD	Control N	Control SMD	Scale	Disease	SMD [95%-CI]	Weight
Low								
Wong, 2016	43	-0.69	41	-0.15	ESAS	HF	-0.41 [-0.84; 0.02]	3.8%
Bekelman, 2015	164	-0.22	167	-0.18	PHQ-9	HF	-0.03 [-0.25; 0.18]	15.4%
Higginson, 2014	42	0.00	40	0.37	HADS	Mixed	-0.37 [-0.81; 0.07]	3.8%
Gade, 2008	186	-0.68	188	-0.56	MCOHPQ Physical	Mixed	-0.11 [-0.32; 0.09]	17.4%
Random effects model							-0.15 [-0.30; 0.01]	--
Heterogeneity: I^2 = 16%, τ^2 = 0.0040, p = 0.31								
High								
Van den Block, 2019	387	0.02	526	0.06	CAD-EOLD	Mixed	-0.04 [-0.18; 0.09]	41.6%
Bekelman, 2018	105	-0.40	105	-0.12	PHQ-9	HF	-0.26 [-0.53; 0.01]	9.7%
Farquhar, 2016	41	-0.14	38	-0.03	HADS	Mixed	-0.11 [-0.55; 0.34]	3.7%
Sampson, 2011	7	-0.46	4	-0.11	Distress VAS	Dementia	-0.20 [-1.43; 1.03]	0.5%
Rabow, 2004	50	-0.45	40	-0.35	U California	Mixed	-0.10 [-0.52; 0.32]	4.1%
Random effects model							-0.09 [-0.20; 0.02]	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.73								
Random effects model							**-0.11 [-0.19; -0.02]**	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.66								
Residual heterogeneity: I^2 = 0%, p = 0.59								



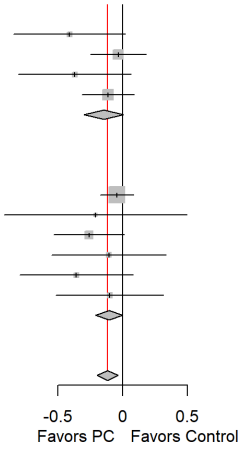
B

Study	Palliative care N	Palliative care SMD	Control N	Control SMD	Scale	Disease	SMD [95%-CI]	Weight
Low								
Wong, 2016	43	-0.69	41	-0.15	ESAS	HF	-0.41 [-0.84; 0.02]	7.3%
Higginson, 2014	42	0.00	40	0.37	HADS	Mixed	-0.37 [-0.81; 0.07]	7.1%
Random effects model							-0.39 [-0.70; -0.08]	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.90								
High								
Farquhar, 2016	41	-0.14	38	-0.03	HADS	Mixed	-0.11 [-0.55; 0.34]	7.0%
Van den Block, 2019	387	0.02	526	0.06	CAD-EOLD	Mixed	-0.04 [-0.18; 0.09]	78.7%
Random effects model							-0.05 [-0.17; 0.08]	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.79								
Random effects model							**-0.15 [-0.34; 0.03]**	--
Heterogeneity: I^2 = 28%, τ^2 = 0.0111, p = 0.25								
Residual heterogeneity: I^2 = 0%, p = 0.96								



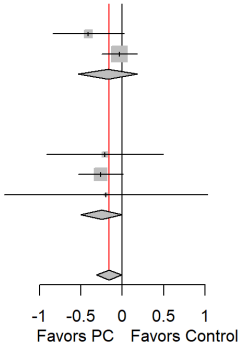
C

Study	Palliative care N	Palliative care SMD	Control N	Control SMD	Scale	Disease	SMD [95%-CI]	Weight
Low								
Wong, 2016	43	-0.69	41	-0.15	ESAS	HF	-0.41 [-0.84; 0.02]	3.7%
Bekelman, 2015	164	-0.22	167	-0.18	PHQ-9	HF	-0.03 [-0.25; 0.18]	14.7%
Higginson, 2014	42	0.00	40	0.37	HADS	Mixed	-0.37 [-0.81; 0.07]	3.6%
Gade, 2008	186	-0.68	188	-0.56	MCOHPQ Physical	Mixed	-0.11 [-0.32; 0.09]	16.6%
Random effects model							-0.15 [-0.30; 0.01]	--
Heterogeneity: I^2 = 16%, τ^2 = 0.0040, p = 0.31								
High								
Van den Block, 2019	387	0.02	526	0.06	CAD-EOLD	Mixed	-0.04 [-0.18; 0.09]	39.7%
O'Donnell, 2018	16	-0.44	15	-0.12	PHQ-8	HF	-0.21 [-0.92; 0.50]	1.4%
Bekelman, 2018	105	-0.40	105	-0.12	PHQ-9	HF	-0.26 [-0.53; 0.01]	9.3%
Farquhar, 2016	41	-0.14	38	-0.03	HADS	Mixed	-0.11 [-0.55; 0.34]	3.5%
Pantilat, 2010	41	-0.53	40	-0.12	Dyspnea	Mixed	-0.36 [-0.80; 0.08]	3.6%
Rabow, 2004	50	-0.45	40	-0.35	U California	Mixed	-0.10 [-0.52; 0.32]	4.0%
Random effects model							-0.11 [-0.21; 0.00]	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.63								
Random effects model							**-0.12 [-0.20; -0.03]**	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.62								
Residual heterogeneity: I^2 = 0%, p = 0.54								



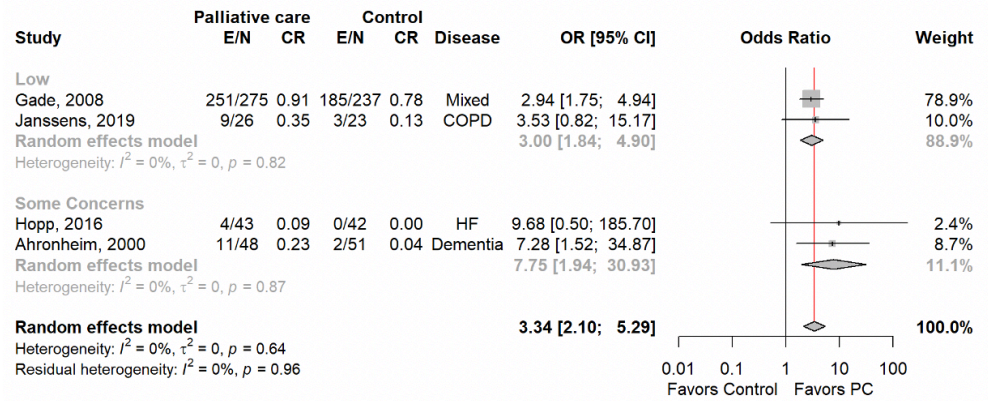
D

Study	Palliative care N	Palliative care SMD	Control N	Control SMD	Scale	Disease	SMD [95%-CI]	Weight
Low								
Wong, 2016	43	-0.69	41	-0.15	ESAS	HF	-0.41 [-0.84; 0.02]	12.4%
Bekelman, 2015	164	-0.22	167	-0.18	PHQ-9	HF	-0.03 [-0.25; 0.18]	50.0%
Random effects model							-0.17 [-0.53; 0.18]	--
Heterogeneity: I^2 = 57%, τ^2 = 0.0405, p = 0.13								
High								
O'Donnell, 2018	16	-0.44	15	-0.12	PHQ-8	HF	-0.21 [-0.92; 0.50]	4.6%
Bekelman, 2018	105	-0.40	105	-0.12	PHQ-9	HF	-0.26 [-0.53; 0.01]	31.4%
Sampson, 2011	7	-0.46	4	-0.11	Distress VAS	Dementia	-0.20 [-1.43; 1.03]	1.5%
Random effects model							-0.25 [-0.50; 0.00]	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99								
Random effects model							**-0.16 [-0.31; -0.01]**	--
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.53								
Residual heterogeneity: I^2 = 0%, p = 0.50								

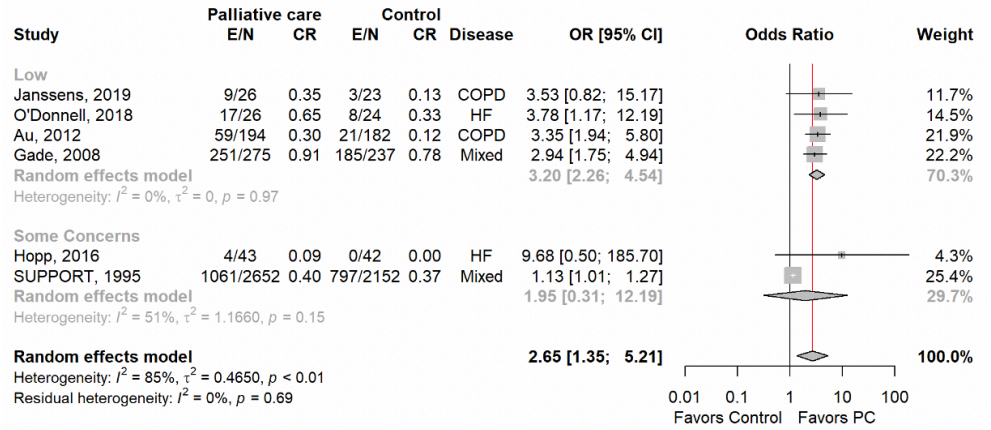


eFigure 2.4. Subgroup Analysis of the Association Between Palliative Care and Advance Care Planning. (A) Interdisciplinary teams involving a physician, (B) Trials of dementia excluded, (C) Trials of mixed disease excluded. Data are presented as the odds and 95% CIs (error bars) of a newly documented advanced care plan during study follow-up. The shaded squares are proportionally sized to reflect study weight and the shaded diamonds represent pooled odds and 95% CIs. The vertical red line indicates the pooled effect estimate, and the black vertical line depicts a null effect. Studies are grouped according to their summary risk of bias (Low, High, Some Concerns). HF – heart failure

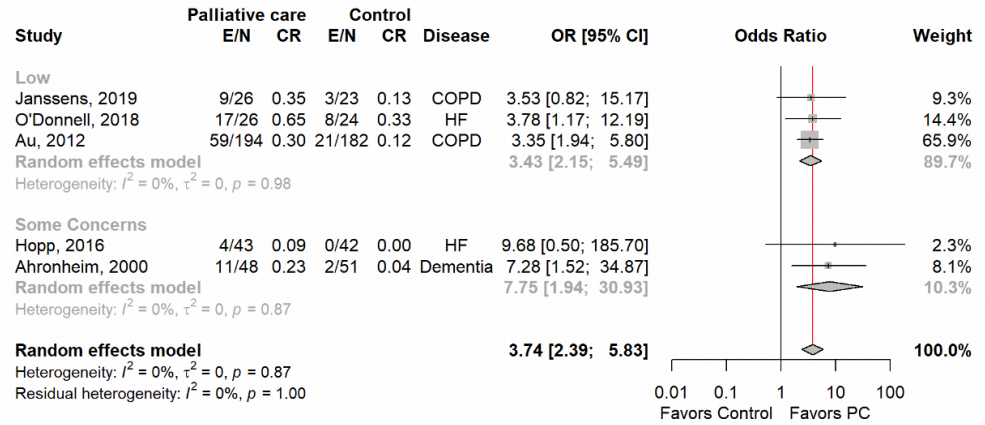
A


Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Low
Gade, 2008 251/275 0.91 185/237 0.78 Mixed 2.94 [1.75; 4.94] 78.9%
Janssens, 2019 9/26 0.35 3/23 0.13 COPD 3.53 [0.82; 15.17] 10.0%
Random effects model 3.00 [1.84; 4.90] 88.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.82
Some Concerns
Hopp, 2016 4/43 0.09 0/42 0.00 HF 9.68 [0.50; 185.70] 2.4%
Ahronheim, 2000 11/48 0.23 2/51 0.04 Dementia 7.28 [1.52; 34.87] 8.7%
Random effects model 7.75 [1.94; 30.93] 11.1%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
Random effects model 3.34 [2.10; 5.29] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64
Residual heterogeneity: I^2 = 0%, p = 0.96
0.01 0.1 1 10 100
Favors Control Favors PC

B

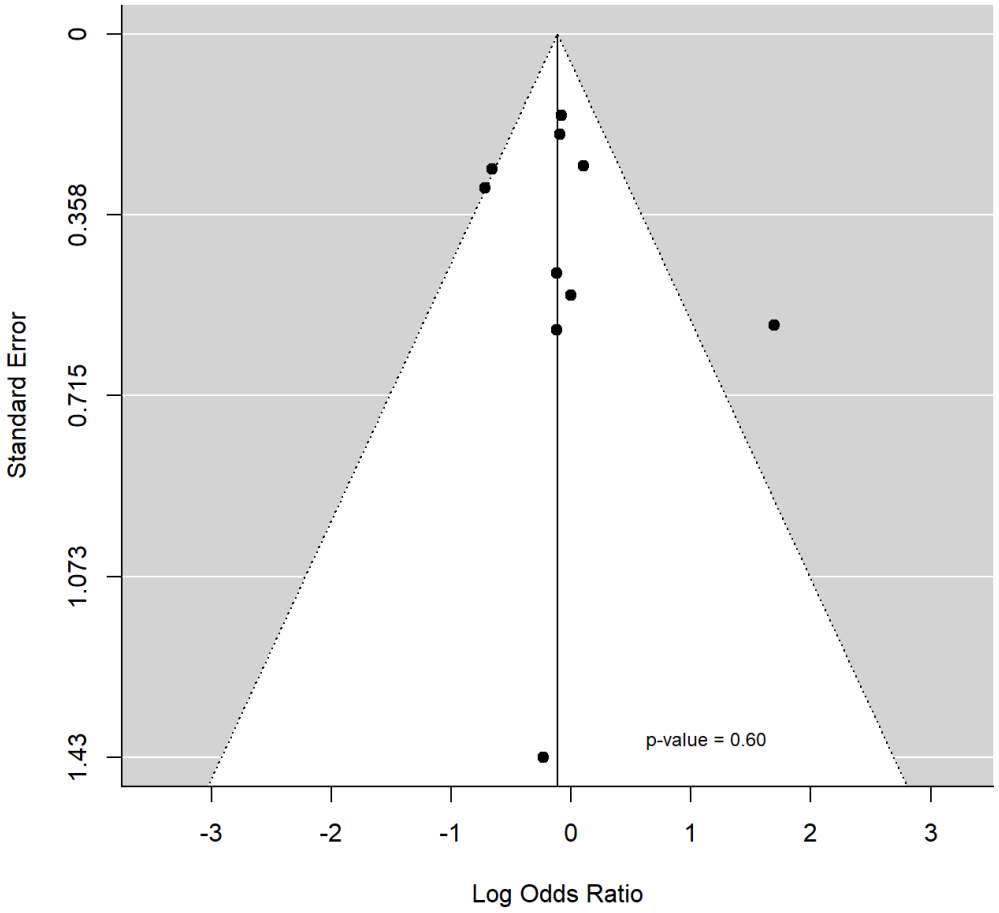

Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Low
Janssens, 2019 9/26 0.35 3/23 0.13 COPD 3.53 [0.82; 15.17] 11.7%
O'Donnell, 2018 17/26 0.65 8/24 0.33 HF 3.78 [1.17; 12.19] 14.5%
Au, 2012 59/194 0.30 21/182 0.12 COPD 3.35 [1.94; 5.80] 21.9%
Gade, 2008 251/275 0.91 185/237 0.78 Mixed 2.94 [1.75; 4.94] 22.2%
Random effects model 3.20 [2.26; 4.54] 70.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.97
Some Concerns
Hopp, 2016 4/43 0.09 0/42 0.00 HF 9.68 [0.50; 185.70] 4.3%
SUPPORT, 1995 1061/2652 0.40 797/2152 0.37 Mixed 1.13 [1.01; 1.27] 25.4%
Random effects model 1.95 [0.31; 12.19] 29.7%
Heterogeneity: I^2 = 51%, τ^2 = 1.1660, p = 0.15
Random effects model 2.65 [1.35; 5.21] 100.0%
Heterogeneity: I^2 = 85%, τ^2 = 0.4650, p < 0.01
Residual heterogeneity: I^2 = 0%, p = 0.69
0.01 0.1 1 10 100
Favors Control Favors PC

C

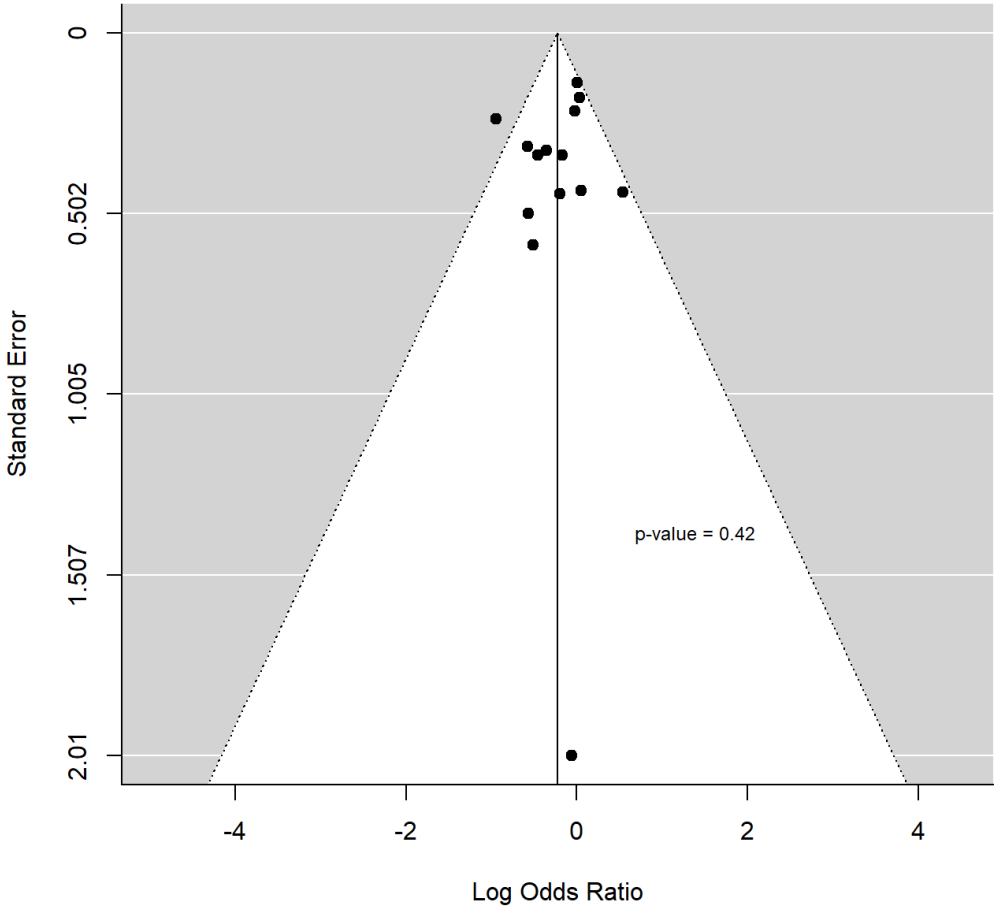

Palliative care
Control
Study
E/N CR E/N CR Disease
OR [95% CI]
Odds Ratio
Weight
Low
Janssens, 2019 9/26 0.35 3/23 0.13 COPD 3.53 [0.82; 15.17] 9.3%
O'Donnell, 2018 17/26 0.65 8/24 0.33 HF 3.78 [1.17; 12.19] 14.4%
Au, 2012 59/194 0.30 21/182 0.12 COPD 3.35 [1.94; 5.80] 65.9%
Random effects model 3.43 [2.15; 5.49] 89.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98
Some Concerns
Hopp, 2016 4/43 0.09 0/42 0.00 HF 9.68 [0.50; 185.70] 2.3%
Ahronheim, 2000 11/48 0.23 2/51 0.04 Dementia 7.28 [1.52; 34.87] 8.1%
Random effects model 7.75 [1.94; 30.93] 10.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
Random effects model 3.74 [2.39; 5.83] 100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
Residual heterogeneity: I^2 = 0%, p = 1.00
0.01 0.1 1 10 100
Favors Control Favors PC

eFigure 2.5. Funnel Plot and Egger Test to Assess the Presence of Publication Bias Among Randomized Clinical Trials Included in the Review. Individual studies are represented by black dots. The solid line represents the pooled estimate of the effect on the outcome. The dashed lines represent the 95% confidence interval of the effect estimate.

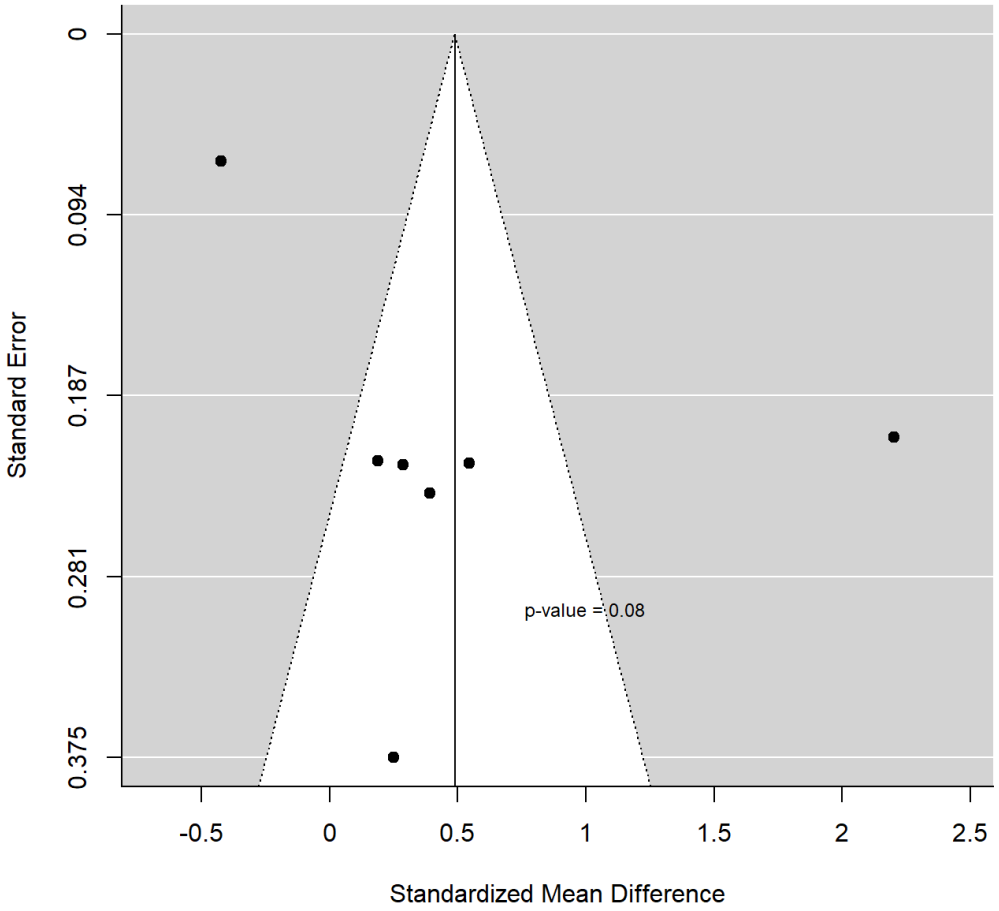
Emergency Department Visits



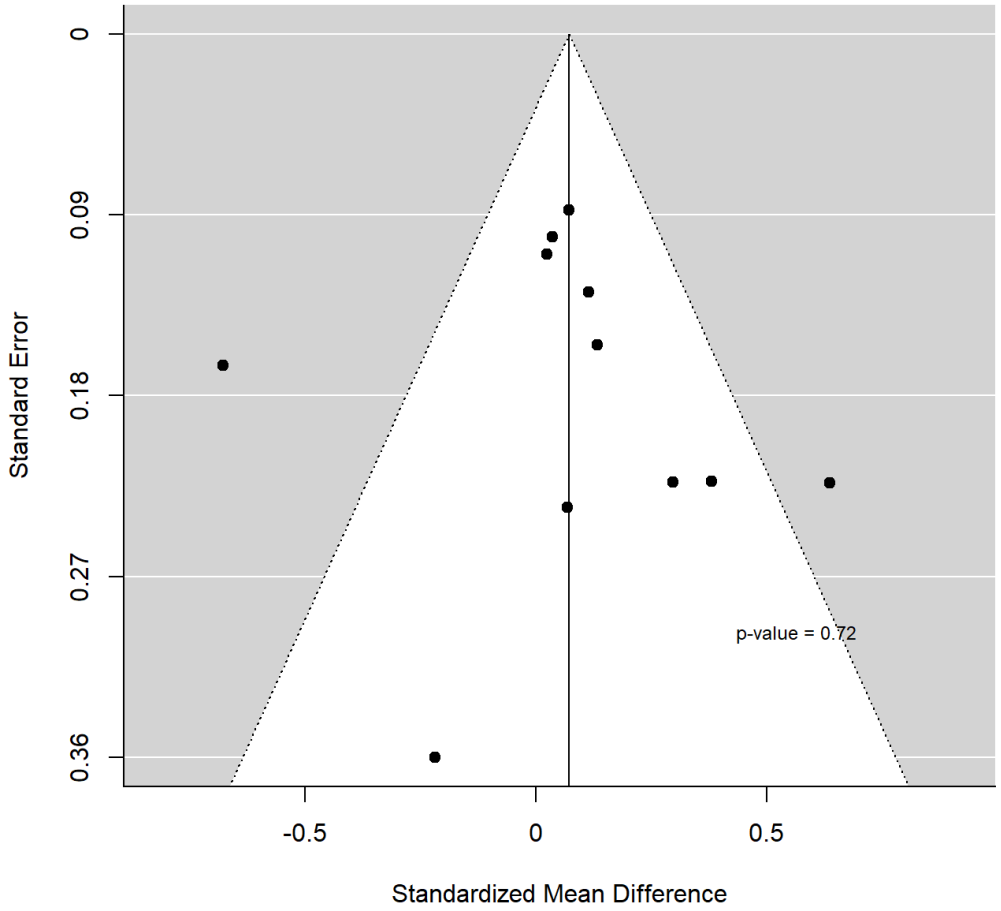
Hospitalization



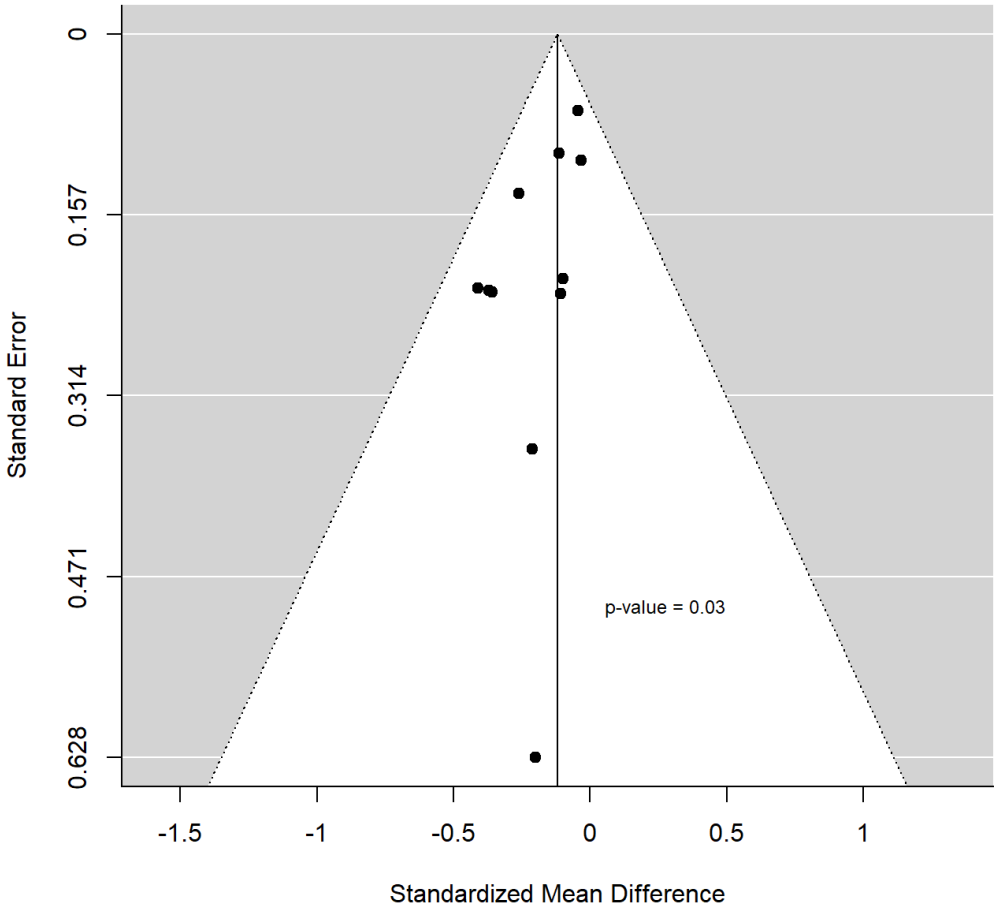
Disease-Generic Quality of Life



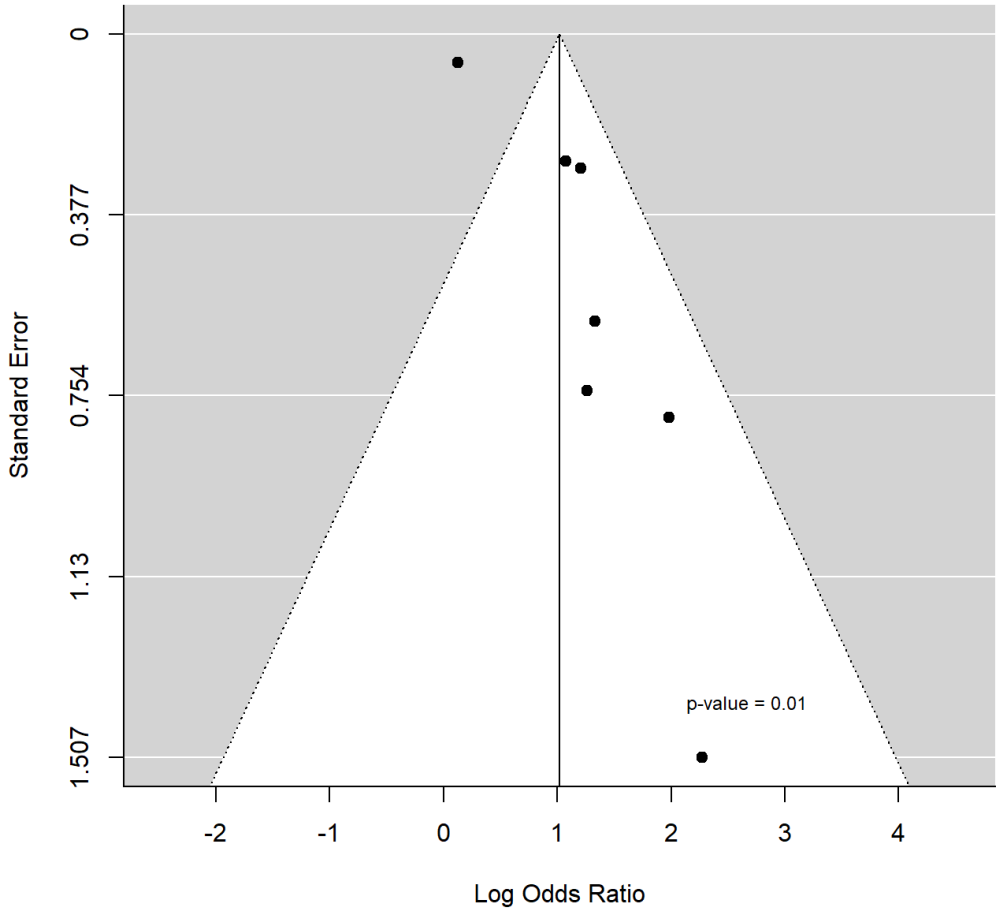
Disease-Specific Quality of Life



Symptoms


Standard Error
0
0.157
0.314
0.471
0.628
p-value = 0.03
-1.5
-1
-0.5
0
0.5
1
Standardized Mean Difference

Advance Care Planning



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3 Study #2 – Association Between Palliative Care and Healthcare Outcomes Among Adults Dying from Noncancer Illness: A Population-Based Matched Cohort Study

3.2 Key Points

What is already known on this topic:

- Patients nearing the end of life often have high rates of potentially avoidable emergency department visits and hospitalizations, which are associated with poor quality of life.
- Palliative care improves the delivery of high-value end-of-life care for patients with cancer, but the evidence for patients with noncancer illness is lacking.

What this study adds:

- Palliative care was associated with 1 less emergency department visit, hospitalization or intensive care unit admission for every 11, 4 and 1 patients dying of chronic organ failure (heart failure, chronic obstructive pulmonary disease, etc.) who received it.
- Palliative care was associated with increased rates of emergency department visits and hospitalization in patients dying of dementia, which differed depending upon whether they lived in the community or in a nursing home.
- These findings highlight the potential benefits of palliative care in select noncancer illness. Scaling existing palliative care to increase access through sustained investment in physician training and current models of collaborative palliative care may improve end-of-life care, which may have significant implications for health policy.

3.3 Abstract

Objective: To measure the association between newly initiated palliative care in the last 6 months of life, healthcare use and location of death in adults dying from noncancer illness; and to compare these associations with those who die from cancer at a population level.

Design: Population-based matched cohort study using linked health administrative data.

Setting: Ontario, Canada between 2010 and 2015.

Participants: 113,540 adults who died of cancer and noncancer illness. Patients were directly matched on cause of death, hospital frailty risk score, the presence of metastatic cancer, residential location (according to 1 of 14 local health integration networks that organize all healthcare services in Ontario), and a propensity-score to receive palliative care that was derived using age and sex.

Exposure: Newly initiated physician-delivered palliative care in the last 6 months of life, administered across all healthcare settings.

Main Outcome Measures: Rates of emergency department visits, hospitalizations, admissions to the intensive care unit (ICU), and odds of death at home versus hospital following first consultation with palliative care, adjusted for patient characteristics.

Results: In patients dying from noncancer illness related to chronic organ failure – similar to cancer – palliative care was associated with statistically significant reduced rates of emergency department visits (crude rate [SD] 1.9 [6.2] versus 2.9 [8.7] per person-year; rate ratio (RR) 0.88 [95% CI 0.85 to 0.91]), hospitalization (crude rate [SD] 6.1 [10.2] versus 8.7 [12.6] per person-year; RR 0.88 [95% CI 0.86 to 0.91]), ICU

admission (crude rate [SD] 1.4 [5.9] versus 2.9 [8.7] per person-year; RR 0.59 [95% CI 0.56 to 0.62]) and increased odds of death at home (n=6,936 (49.5%) versus n=9,526 (39.6%); odds ratio 1.67 [95% CI 1.60 to 1.74]). In patients dying of dementia, palliative care was associated with increased rates of emergency department visits (crude rate [SD] 1.2 [4.9] versus 1.3 [5.5] per person-year; RR 1.06 [95% CI 1.01 to 1.12]), hospitalization (crude rate [SD] 3.6 [8.2] versus 2.8 [7.8] per person-year; RR 1.33 [95% CI 1.27 to 1.39]) and reduced odds of dying at home or in a nursing home (n=6,667 (72.1%) versus n=13,384 (83.5%); OR 0.68 [95% CI 0.64 to 0.73]), which differed depending upon whether they lived in the community or in a nursing home.

Conclusions: These findings highlight the potential benefits of palliative care in select noncancer illness. Scaling existing palliative care to increase access through sustained investment in physician training and current models of collaborative palliative care may improve end-of-life care, which may have significant implications for health policy.

3.4 Introduction

Patients nearing the end of life often have high rates of costly healthcare including potentially avoidable emergency department visits and hospitalizations.[11] These potentially burdensome interventions are often avoidable and associated with poor quality of life.[3,8–11,15,132,133] Consequently, the demand for palliative care is rapidly growing. The primary goal of palliative care is to improve quality of life and reduce symptom burden. Although not its intended purpose, one of the potentially beneficial consequences of palliative care may be to simultaneously maximize high-value care by reducing healthcare use and its associated costs.[69,127]

Current evidence for the many benefits of palliative care are skewed toward patients with cancer. A recent systematic review and meta-analyses of randomized controlled trials of palliative care interventions reported that healthcare use was significantly decreased in 11 of 24 trials that measured this outcome. However, among all 43 trials included in the systematic review, nearly 70% were conducted in patients with cancer.[69] This may limit the evidence's applicability to those with noncancer illness who have a trajectory of dying marked by frequent exacerbations and subsequent patterns of healthcare use.[65,69,80–82,134] This unpredictable trajectory can make it difficult for patients and their healthcare providers to decide when to focus on a more comfort-oriented approach to care. Research examining the role of palliative care on healthcare use in noncancer illness primarily comes from a limited number of studies of patients with heart failure, dementia or mixed illness, and there is conflicting evidence as to whether it reduces overall healthcare use.[69,98,100–102,104,105,108,111–113,116,118,119]

This study is novel because it examines the role of palliative care on healthcare use near the end of life in patients dying of noncancer illness at a population level in a large healthcare system. Whereas a prior population-level study examined home-based palliative care,[135] our study examines palliative care delivered across all care settings. This focus on noncancer illness is distinct from studies that have previously measured patient reported outcomes such as quality of life or healthcare use in patients with cancer. For healthcare systems to achieve the greatest value for patient's at or approaching end-of life (i.e. to improve patient experience and population health while reducing costs), it is important to first define who may derive potential benefits from palliative care. The objective of this study was to measure the association between newly initiated physician-delivered palliative care in the last 6 months of life and healthcare use in adults dying from noncancer illness, and to compare these associations with those who die from cancer.

3.5 Methods

Study Design, Setting and Data Sources

We conducted a population-based cohort study in Ontario, Canada, using linked clinical and health administrative databases. Ontario is Canada's most populous province with over 10 million adults. All residents of Ontario have access to hospital care, physicians' services without the requirement for co-payment, and those aged ≥ 65 years of age are provided universal prescription drug insurance coverage. The administrative datasets used in this study were linked using encoded identifiers at the patient level at ICES (formerly the Institute of Clinical and Evaluative Sciences) (eText 3.1). These datasets are routinely used to conduct studies involving palliative care.[11,46,136–138] Ethics approval was obtained from Sinai Health System's research ethics board (ID 18-0015-E).

Study Cohort

Our decedent cohort included all Ontario adults (age ≥18 years) who died from cancer or selected noncancer causes between January 1st, 2010 and December 31st, 2015. Cause of death was determined according to the ICD-10 code that identified the disease that directly caused death as indicated by a physician on their death certificate. We defined noncancer illness as death due to heart failure (HF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), cirrhosis, stroke or dementia because these diseases represent the most common noncancer conditions and some are also the most well-studied in the palliative care literature.[69–71] For primary analysis, we further subdivided those who died of noncancer illness into chronic organ

failure (HF, COPD, ESRD, cirrhosis and stroke) or frailty (dementia), which are recognized as unique trajectories of functional decline at the end of life and may influence a person's healthcare needs and subsequent use.[65,80–82] For example, patients dying of cancer have a readily identifiable inflection point in their disease trajectory following the failure of adjuvant therapies, which may trigger palliative care referral earlier in the disease course. Conversely, it may be more difficult to determine when to institute therapies aimed primarily at enhancing quality of life in patients with chronic organ failure and frailty who suffer dramatic exacerbations of their underlying disease with incomplete recovery on a background of progressive decline toward death.

Initiation of Palliative Care

The primary exposure was a person's first encounter with palliative care across all care settings within the last 6 months of life, which served as the study index date. We chose the last 6 months of life instead of the last year in order to minimize the effects of confounding by indication due to time-varying covariates. We identified the delivery of palliative care based on a set of unique physician claims fee codes (eText 3.3).[11,46–48,65,133,136,138–140] These codes were created to specifically indicate the delivery of palliative care and are related to therapies not intended to be curative, such as symptom management or counselling.

In Ontario, over 70% of palliative care is delivered by general practitioners, which includes both generalist and specialist palliative care physicians.[139] A physician was deemed to be a palliative care specialist their annual billing is comprised of >10% of palliative care fee codes, which is based on a previously validated method with a

sensitivity of 76.0% and specificity of 97.8%.[139] Formal palliative care is predominantly provided by physicians and nurse practitioners in hospitals, outpatient clinics, and the home, and also includes home care services (such as nursing care and personal support workers). In general, patients require a referral from one of their physicians to access specialized palliative care services. Palliative care can also be provided by generalists (e.g., family doctor or other non-palliative care specialists) without a referral.

Patient Characteristics

We measured demographic and clinical variables including age, sex, socioeconomic status, rural location of residence, comorbidities and chronic conditions,[141] and hospital frailty risk score,[142] using a 5-year look back period. We also measured year of death, use of acute health care services in the one year before the study index date, and the timing of first palliative care consultation (or matched date in nonexposed patients) relative to death. We also determined the presence of functional decline in the year before the index date in a subset of adults who had completed home care assessments (eText 3.2). In patients who died from dementia, we determined if they were living in a nursing home using a 5-year lookback for the dispensing of at least 1 medication in a nursing home during that time.[143]

Matching

To minimize confounding by indication newly initiated palliative care, patients were directly matched 1:2 using baseline characteristics measured at six months prior to death. We directly matched on: 1) cause of death, 2) frailty score category, 3)

presence of metastatic cancer, 4) residential region (according to 1 of 14 local health integration networks), and 5) the probability of receiving palliative care using a propensity-score derived from age and sex. When more than 2 matched controls were available, we chose those with the closest year of death. Patients who did not receive palliative care (controls) were assigned the corresponding matched case index date to ensure equal follow-up time. We matched at 6 months prior to death rather than at study index date. Study index date was unique to each patient and it would be computationally too intensive to assign controls an index date and then iteratively find a match with the same index date for a case.

Outcomes

The primary outcomes were the rates of healthcare use, including unplanned ED visits, hospitalization and ICU admission following the study index date. Secondary outcomes were the location of death, which included hospital, home (including in a nursing home), or other (eText 3.4). Deaths that occurred in a dedicated palliative care unit (PCU) or hospice were categorized as 'other' because they cannot be distinguished from other subacute care beds such as those in a rehabilitation hospital. Currently, it is estimated that there are only 4,300 PCU and hospice beds in Ontario.[54] Other secondary outcomes included the rates of potentially burdensome interventions,[132] defined as positive pressure ventilation, cardiopulmonary resuscitation and the initiation of dialysis (eText 3.5). We specifically chose these interventions because they are common, costly, associated with discomfort, are of limited benefit at the end of life and are easily measured as quality indicators of end-of-life care using

administrative data.[144] Incident use of dialysis was determined using a 1-year lookback from the index date to ensure that there was no prior exposure.

Statistical Analysis

The association between palliative care and the rates of healthcare use, potentially burdensome interventions and location of death were estimated using multivariable generalized linear models (GLM), accounting for matching. Outcomes for count data were modelled using a stratified Poisson GLM approach (unplanned ED visits, hospitalization, ICU admission and potentially burdensome interventions); whereas, multilevel categorical outcomes were modelled using a multinomial logistic GEE approach (location of death - death at home versus hospital). All models were adjusted for age, sex, comorbidities, rurality, neighborhood income, hospital frailty risk score, and total number of hospitalizations in the one year prior to index date. The hospital frailty risk score (range 0-50) is a comprehensive and validated measure of a person's function and comorbidity that reflects global illness severity and identifies a group of patients who are at greater risk of adverse outcomes including hospitalization and 30-day mortality.[142] We categorized hospital frailty measures into 4 groups based on the distribution of scores within our cohort: 0, 0.1-8.9, ≥9 and not hospitalized.[142,145] We did not account for clustering by physician or facility since most people receive end-of-life care from many physicians in multiple care settings. We performed two pre-specified subgroup analyses that measured the primary outcome by cancer as well as by individual cause of death. We performed a post-hoc analysis of healthcare use and location of death among those who died of dementia, stratified by residence in a nursing

home. To provide a comparison of the outcomes between patients who died of cancer versus noncancer illness, we evaluated for effect modification by cause of death (cancer versus organ failure versus dementia) as an interaction term, with palliative care as the predictor variable.

To translate our findings into a more clinically meaningful measure, we calculated the associated number needed to treat (NNT) for each healthcare use outcome for patients who received and did not receive palliative care. Using methods developed by Austin, we calculated the crude rate difference of ED visits, hospitalizations and ICU admissions after bootstrapping randomly selected sets of paired patients 1000 times. From the estimated crude rate difference and variance in each bootstrap sample, we then used the inverse to calculate the NNT and corresponding 95% CIs.[146]

We report balance diagnostics in our propensity-score matched cohort using weighted standardized differences to account for the 1:2 matching over statistical tests to assess balance between groups which are confounded with sample size.[147]
All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Patient and Public Involvement

Multiple patients with chronic serious illness were informally asked if they felt the results reported herein were reflective of their illness experience to check the validity of the findings.

3.6 Results

Baseline Characteristics

There were 260,762 adults who died of cancer and noncancer illness during the study period. Among these, 71,815 adults were excluded. The final cohort consisted of 113,540 adults; 63,320 (55.8%) who died of noncancer illness (Figure 3.1). Subjects in the cohort were a median age of 83 years, 53.6% were female and the median hospital frailty risk score was 4 (IQR 1-11) (Table 3.1 and eTable 3.1). Among those with dementia, 72.1% (18,254) lived in a nursing home.

At six months prior to death the baseline characteristics were similar between patients dying of noncancer illness who received (cases) and did not receive (controls) palliative care; however, by the index date when cases received their first palliative care visit, some differences arose between cases and controls. A higher proportion of people receiving palliative care lived in urban areas, had multiple chronic conditions including metastatic cancer, and had frailty scores ≥9 compared to those that did not receive palliative care. Patients receiving palliative care also had a higher number of hospitalizations and ED visits in the year prior (Table 3.2 and eTable 3.2).

Healthcare Use

In patients dying of chronic organ failure, palliative care was associated with reduced rates of emergency department visits (crude rate [SD] 1.9 [6.2] versus 2.9 [8.7] per person-year; adjusted rate ratio (aRR) 0.88 [95% CI 0.85 to 0.91]), hospitalization (crude rate [SD] 6.1 [10.2] versus 8.7 [12.6] per person-year; aRR 0.88 [95% CI 0.86 to 0.91]), and ICU admission (crude rate [SD] 1.4 [5.9] versus 2.9 [8.7] per person-year;

aRR 0.59 [95% CI 0.56 to 0.62]), compared to those who did not receive palliative care. In patients dying of dementia, palliative care was not associated with reduced rates of ICU admission (crude rate [SD] 0.2 [2.1] versus 0.2 [2.1] per person-year; aRR 1.03 [95% CI 0.96 to 1.11]) but was associated with increased rates of emergency department visits (crude rate [SD] 1.2 [4.9] versus 1.3 [5.5] per person-year; aRR 1.06 [95% CI 1.01 to 1.12]) and hospitalization (crude rate [SD] 3.6 [8.2] versus 2.8 [7.8] per person-year; aRR 1.33 [95% CI 1.27 to 1.39]). However, there were differences in these outcomes noted depending on whether the patient resided in a nursing home or not, as no association was found for patients dying from dementia who resided in the community (eTables 3.5 and 3.6). The magnitude of all associations were similar in those dying from cancer compared to chronic organ failure, except for rates of ICU admission which was smaller in cancer: emergency department visits (crude rate [SD] 2.5 [6.7] versus 3.4 [8.4] per person-year; aRR 0.89 [95% CI 0.86 to 0.91]), hospitalization (crude rate [SD] 5.5 [8.8] versus 7.5 [10.2] per person-year; aRR 0.82 [95% CI 0.80 to 0.83]), and ICU admission (crude rate [SD] 0.4 [2.9] versus 2.2 [6.8] per person-year; aRR 0.22 [95% CI 0.21 to 0.23]) (Figure 3.2). Based on these results, palliative care was associated with 1 less ED visit, hospitalization or ICU admission for every 11 (95% CI 6 to 32), 4 (95% CI 3-5) and 1 (95% CI 1 to 2) patients dying from chronic organ failure who received it, respectively.

When we evaluated for the effect of cancer compared to noncancer (organ failure or dementia) related deaths on healthcare use outcomes, we found variable results (eTable 3.9).

Hospitalized patients had similar lengths of stay regardless of whether they received palliative care or not (7.8 ± 14.1 versus 6.3 ± 11.4 days, respectively).

Location of Death

Overall, 40,626 (35.8%) of patients died in hospital or ICU. Patients who died from chronic organ failure and received palliative care had a higher odds of dying at home or in their nursing home (NH) than in hospital, compared to those who did not receive palliative care (n=6,936 (49.5%) versus n=9,526 (39.6%); adjusted odds ratio (aOR) 1.67 [95% CI 1.60 to 1.74]). In patients dying from dementia, palliative care was associated with a decreased odds of death at home or in the NH (n=6,667 (72.1%) versus n=13,384 (83.5%); aOR 0.68 [95% CI 0.64 to 0.73]. However, there was an associated increased odds of death at home for patients dying of dementia who resided in the community (aOR 1.35 [95% CI 1.23 to 1.49]) (eTable 3.6). The magnitude of the association was higher among those dying from cancer (aOR 2.83 [95% CI 2.73 to 2.94] compared to those dying from noncancer illness (Figure 3.2).

Potentially Burdensome Interventions

Patients dying from chronic organ failure who received palliative care had a lower associated rate of potentially burdensome interventions compared to those who did not receive palliative care (composite aRR 0.66 [95% CI 0.64 to 0.69]). In patients dying of dementia, palliative care was associated with an increased rate of potentially burdensome interventions (aRR 1.18 [95% CI 1.08 to 1.31]). The magnitude of the

association was smaller for patients dying from cancer (aRR 0.27 [95% CI 0.26 to 0.28]) (eTables 3.3 and 3.4 and eFigure 3.1).

3.7 Discussion

Principle Findings

We conducted a matched population-based study of 113,540 adults in Ontario, Canada who died from cancer and noncancer illness. We found that in those dying from chronic organ failure, physician-delivered palliative care was associated with a 12%, 12% and 41% reduction in the rate of emergency department visits, hospitalizations and ICU admissions, respectively. Palliative care was also significantly associated with a 1.67 increased odds of death at home. We compared these associations between different trajectories of dying and found similar results in those dying from cancer. Unexpectedly, we found increased rates of healthcare use associated with palliative care in those dying from dementia, which differed between those who resided in a nursing home compared with those who lived in the community.

Policy Implications

Patients, caregivers and healthcare systems struggle with the growing burden of medical complexity that is also associated with poor quality of life and high healthcare expenditure.[3,8–11,15,132,133,148] End-of-life care that involves hospitalization and ICU admission is costly and potentially burdensome. Our study supports the role of palliative care in providing high-value end-of-life care to people dying with cancer and most noncancer illness.[127] We found that palliative care may reduce healthcare use and potentially burdensome interventions near the end of life. We also found an association between palliative care and an increased odds of dying at home – a place that most people prefer and a recognized indicator of high-quality end-of-life care.[51–53] Our

findings are consistent with prior literature on the association between home-based palliative care and healthcare use outcomes and location of death in patients with cancer, and add to the knowledge about the associated effects in noncancer illness across all care settings.[133,135]

Comparison with Other Studies

Most of the evidence measuring the effect of palliative care and healthcare use in noncancer illness is limited to small studies of patients with heart failure, dementia, or mixed illness and is conflicting.[69,98,100–102,104,105,108,111–113,116,118–120] There are 14 randomized control trials (RCTs) that employ palliative care interventions and measure its effect on rates of ED visits and hospitalization. Three out of eight of these studies demonstrated a reduction in ED visits, and one out of 13 demonstrated a reduction in hospitalization. However, the interventions were heterogeneous in their design, the measures were all secondary analyses, and many of the trials were at high risk of bias and not powered to detect differences in these specific outcomes. Similar to our findings, a propensity-matched cohort study of 6,218 patients primarily with cancer (80%) but also noncancer illness (20%) in the last 6 months of life in Ontario, Canada found that community-based palliative care was associated with a 33% lower risk of emergency department visits and hospitalizations.[133] Approximately 35% of our cohort died in hospital, which is similar to findings from a recent study in a large healthcare system.[56] Our study extends these findings to patients with noncancer illness at a population-level in a universal healthcare system that includes palliative care delivered across all care settings.

Strengths and Limitations

Our study is limited by the lack of information on patient and caregiver preferences for care, which we believe is paramount to providing high-quality patient goal-directed palliative care. We assumed that patients received palliative care for issues related to their cause of death. In reality, many of these complex patients had multiple comorbidities, possibly including cancer, which likely contributed to their overall palliative needs. Prior work also demonstrates that patients with metastatic cancer are more likely to receive palliative care than other disease groups.[65,136] The observed heterogeneity in healthcare outcomes among the subgroups of patients dying of chronic organ failure may relate to differences in their underlying palliative (e.g. symptoms) and non-palliative care (e.g. difference in needs during an exacerbation of their underlying disease such as ongoing dialysis) needs. Patients who received palliative care were generally sicker than those who did not, which may underestimate the magnitude of our results as these patients may be more likely to have higher healthcare use. We used robust statistical methods to minimize the risk of confounding by indication, and consequently found only marginal differences between our unadjusted and adjusted results. To further minimize these effects, we made several decisions intended to minimize this risk, including: matching on several factors strongly associated with exposure to palliative care; the use of a cohort of patients who were in the last 6 months of life (to minimize the effects due to time-varying covariates and because baseline patient variables achieved a better balance at 6 compared to 12 months); and a “new-user” design to increase the likelihood that the groups of patients would be similar at

baseline. However, patients with advanced illness often receive late referral to palliative care services that may limit several opportunities to relieve potentially avoidable suffering. Current recommendations from several societies encourage the integration of palliative care early in the course of a person's disease, instead of at the end of life.[134,149,150] In regions of limited healthcare access, some patients may not be able to receive care at home and avoid potential transfers to the ED or hospital, regardless of their preferences. Ontario lacks the rich infrastructure of hospice networks like those found in many areas of the United States, which may limit the ability of patients with significant care needs to die outside of the hospital setting.[136] We also measured a physician-delivered "palliative approach" to care across all care settings that includes both generalist and specialist palliative care physicians. While this likely strengthens its generalizability to real-world care, it may underestimate the magnitude of the association for specialized palliative care delivered in the home.[46] In other jurisdictions like the US which use different funding mechanisms such as the Medicare Hospice Benefit, palliative care may be delivered by healthcare providers other than physicians, which may include nurse practitioners or social workers.[98] Delivery of care by these providers and its association with important outcomes is not captured in our study using physician fee claims. However, the use of fee codes in administrative data as a means to capturing delivery of palliative care is a strength of our study given that care classification has been less successful in health systems without universal coverage.[151] Finally, utilizing the information on a patient's death certificate was intentionally selected to maximize specificity, but likely decreased the overall denominator in our study population. While this may result in inflated confidence intervals, we still found

significant differences in many outcomes. We were especially concerned that other approaches may introduce too much heterogeneity and other sources of bias.

Unanswered Questions

Questions remain regarding the timing, location of initiation and models of care of palliative care delivery to optimize end-of-life care for patients with noncancer illness, including the involvement of a patient's primary care provider in the delivery of palliative care that is often founded upon a longitudinal and trusting relationship. Further study is also required to explain the differences found in healthcare use between patients dying with cancer and chronic organ failure compared to those dying from dementia. One explanation may be that many care decisions in patients with dementia are made by substitute decision makers and not the patients themselves. Dementia is often not recognized as a terminal illness in the same way as are chronic organ failure and cancer, which makes it difficult to know when to focus on comfort over prolongation of life. It may also be more challenging to recognize the cause of death as dementia in patients dying of its related complications (e.g. pneumonia) when their dementia is less severe, compared to those with cancer. This may limit the generalizability of our results to those with milder disease, such as those earlier in the course of their disease trajectory. Alternatively, a palliative care physician may have been involved in situations involving complicated goals of care discussions if there was discordance in care plans between the patient or caregiver and their treating physicians. Prior work demonstrated a concerning rate of potentially burdensome interventions delivered in acute care settings near the end of life in this vulnerable population, especially for those who reside

in a nursing home.[132,152,153] In our study, 72.2% of patients who died from dementia lived in a nursing home. We speculate that our findings may be related to differences in the care provided in nursing homes from that in the community. Multiple factors such as family pressure, physician workload, the capability of nursing home staff, and potential medico-legal concerns influence decisions to go to acute care, especially in the nursing home setting where many patients with dementia reside.[154]

3.8 Conclusions

Palliative care was associated with reduced rates of healthcare use and an increased likelihood of a home death in people dying of chronic organ failure, but not dementia. These findings highlight the potential benefits of palliative care in select noncancer illness. Scaling existing palliative care to increase access through sustained investment in physician training and current models of collaborative palliative care may improve end-of-life care, which may have significant implications for health policy.

Figure 3.1 – Flow diagram for the creation of the study sample. All adults who died from heart failure (HF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), stroke, dementia or cancer were assessed for inclusion in the study. Patients who received their first consultation with palliative care at least 7 days prior to death were included and matched 1:2 to patients who did not receive palliative care. OHIP-Ontario Health Insurance Plan

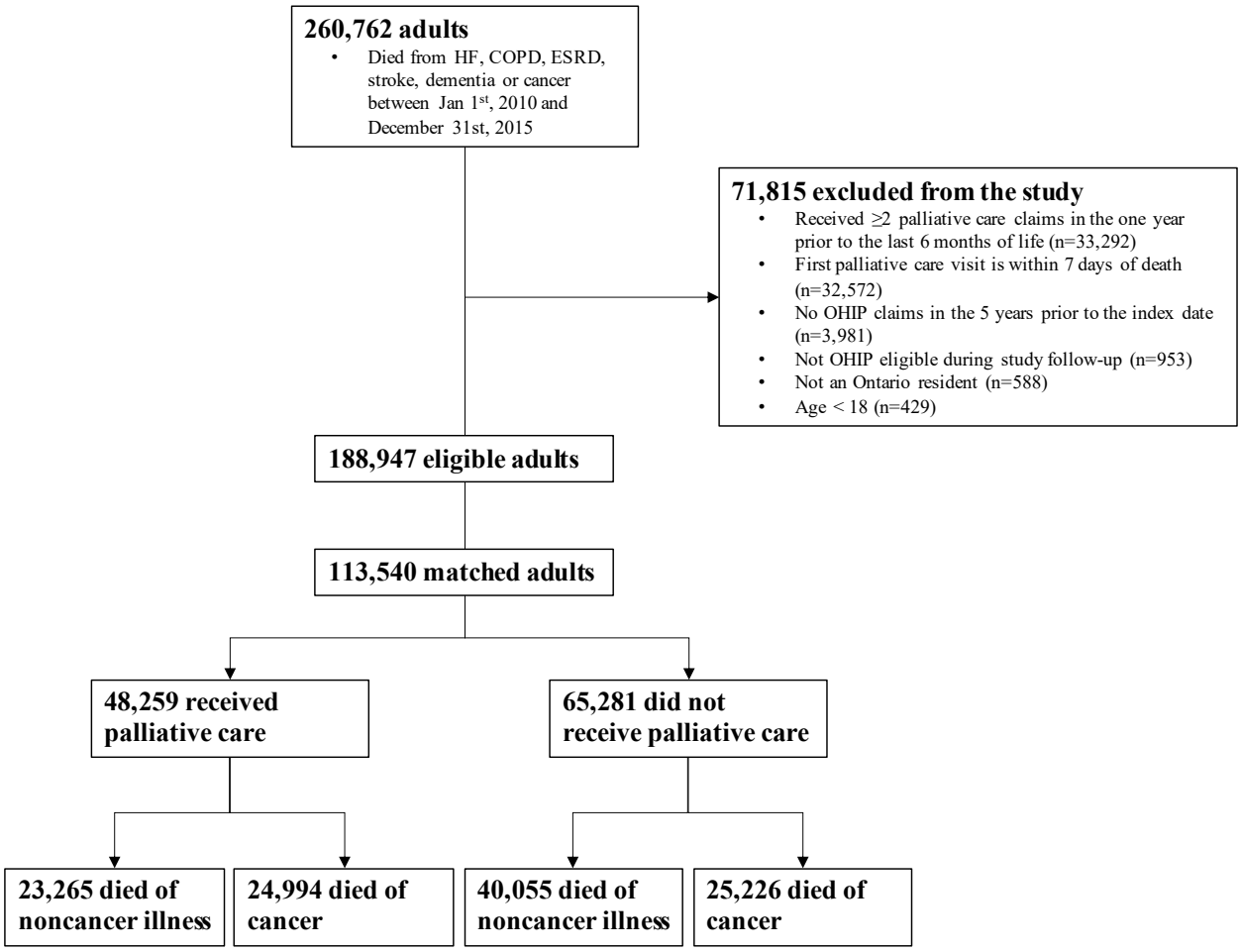


Figure 3.2 – Association between palliative care and healthcare use. Association between newly initiated palliative care and rates of (A) emergency department visits not resulting in hospitalization, (B) hospitalization, and (C) intensive care unit admissions or (D) location of death among adults in the last 6 months of life dying from cancer and noncancer illness in Ontario between 2010 and 2015. The locations of death were home (including nursing home), acute care (including hospital and ICU), and other. Models were adjusted for age, sex, comorbidities, rurality, neighborhood income, frailty and hospitalizations in the year prior to index date.

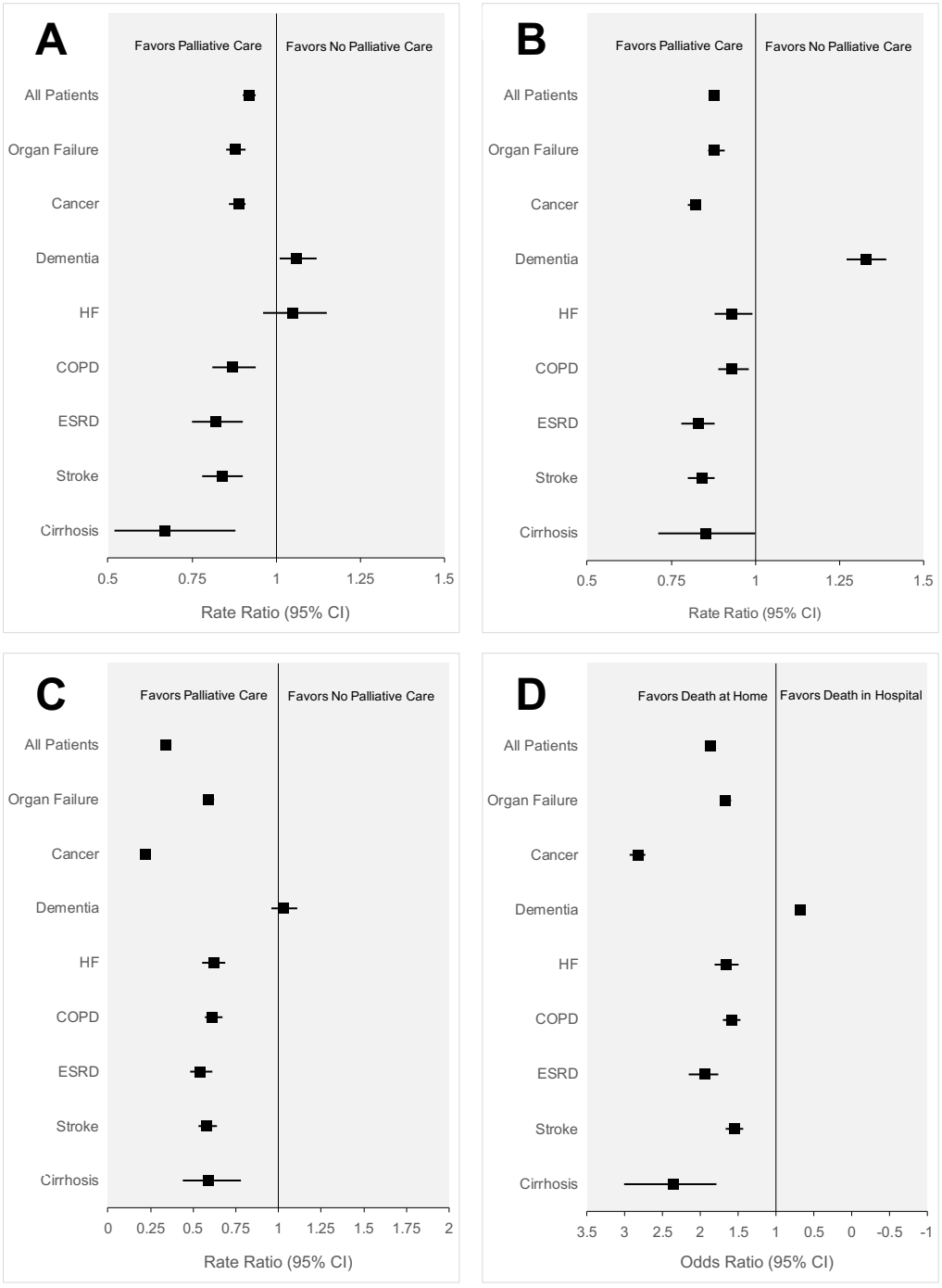


Table 3.1 – Baseline characteristics *at 6 months prior to death* of matched patients in the last 6 months of life who died of noncancer illness in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 23,265)	**No (n = 40,055)**	**Weighted Standardized Difference**
Age in years, mean (SD)	84.3 (9.0)	84.1 (8.9)	0.00
Female sex, n (%)	13,700 (58.9)	23,590 (58.9)	0.00
Cause of death, n (%)			
COPD	4,094 (17.6)	7,800 (19.5)	0.00
Dementia	9,255 (39.8)	16,023 (40.0)	0.00
Cirrhosis	333 (1.4)	516 (1.3)	0.00
ESRD	2,339 (10.1)	3,607 (9.0)	0.00
Congestive heart failure	2,768 (11.9)	4,261 (10.6)	0.00
Stroke	4,476 (19.2)	7,848 (19.6)	0.00
Rural, n (%)	2,409 (10.4)	5,806 (14.5)	0.09
Hospital Frailty Score, n (%)			
Mean (SD)	8.9 (8.5)	8.7 (8.3)	0.00
Median (IQR)	7 (2-14)	7 (2-13)	0.00
0	2,721 (11.7)	4,723 (11.8)	0.00
0.1-8.9	8,390 (36.1)	14,513 (36.2)	0.00
9+	7,503 (32.3)	12,589 (31.4)	0.00
Not hospitalized	4,651 (20.0)	8,230 (20.5)	0.00
Chronic Conditions			
Arrhythmia	5,227 (22.5)	7,969 (19.9)	0.05
Cancer			
Primary	1,494 (6.4)	2,117 (5.3)	0.05
Metastatic	66 (0.3)	82 (0.2)	0.00
COPD	4,640 (19.9)	7,681 (19.2)	0.04
Congestive heart failure	4,691 (20.2)	7,146 (17.8)	0.05
Coronary artery disease	3,963 (17.0)	6,140 (15.3)	0.04
Dementia	4,881 (21.0)	9,570 (23.9)	0.08
Diabetes	4,926 (21.2)	8,413 (21.0)	0.01
Hypertension	19,444 (83.6)	32,720 (81.7)	0.04
Renal disease	2,653 (11.4)	3,859 (9.6)	0.04

Rheumatoid arthritis	800 (3.4)	1,174 (2.9)	0.03
Stroke	2,578 (11.1)	4,114 (10.3)	0.02
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	15 (9-21)	15 (9-22)	0.01
Emergency department visits	1 (0-2)	0 (0-2)	0.13
Hospitalizations	0 (0-1)	0 (0-1)	0.12

COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range

Table 3.2 – Baseline characteristics *at date of first palliative care visit (index date)* of matched patients in the last 6 months of life who died of noncancer illness in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 23,265)	**No (n = 40,055)**	**Weighted Standardized Difference**
Age in years, mean (SD)	84.6 (9.0)	84.5 (8.9)	0.00
Female sex, n (%)	13,700 (58.9%)	23,590 (58.9%)	0.00
Cause of death, n (%)			
COPD	4,094 (17.6%)	7,800 (19.5%)	0.00
Dementia	9,255 (39.8%)	16,023 (40.0%)	0.00
Cirrhosis	333 (1.4%)	516 (1.3%)	0.00
ESRD	2,339 (10.1%)	3,607 (9.0%)	0.00
Congestive heart failure	2,768 (11.9%)	4,261 (10.6%)	0.00
Stroke	4,476 (19.2%)	7,848 (19.6%)	0.00
Rural, n (%)	2,424 (10.4%)	5,784 (14.4%)	0.09
Hospital Frailty Score, n (%)			
Mean (SD)	12.3 (9.2)	10.1 (8.7)	0.30
Median (IQR)	11 (5-18)	8 (3-15)	0.30
0	1,220 (5.2%)	3,523 (8.8%)	0.14
0.1-8.9	7,766 (33.4%)	13,945 (34.8%)	0.02
9+	11,859 (51.0%)	15,205 (38.0%)	0.24
Not hospitalized	2,420 (10.4%)	7,382 (18.4%)	0.21
Chronic Conditions			
Arrhythmia	6,914 (29.7%)	9,135 (22.8%)	0.14
Cancer			
Primary	1,859 (8.0%)	2,269 (5.7%)	0.09
Metastatic	379 (1.6%)	158 (0.4%)	0.11
COPD	5,768 (24.8%)	8,593 (21.5%)	0.10
Congestive heart failure	6,495 (27.9%)	8,497 (21.2%)	0.14
Coronary artery disease	4,803 (20.6%)	6,670 (16.7%)	0.09
Dementia	7,900 (34.0%)	11,201 (28.0%)	0.12
Diabetes	5,908 (25.4%)	8,999 (22.5%)	0.06

Hypertension	19,811 (85.2%)	32,975 (82.3%)	0.06
Renal disease	3,705 (15.9%)	4,566 (11.4%)	0.11
Rheumatoid arthritis	817 (3.5%)	1,190 (3.0%)	0.03
Stroke	4,778 (20.5%)	5,120 (12.8%)	0.20
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	17 (10-24)	16 (10-23)	0.06
Emergency department visits	2 (1-3)	1 (0-2)	0.36
Hospitalizations	1 (0-2)	0 (0-1)	0.44
Functional Decline[b]	8,978 (38.6%)	9,551 (23.8%)	0.32
Physician Type n,(%)			
General Practitioner	19,778 (85.0)	--	--
Specialist	3,487 (15.0)	--	--
Palliative Care Specialist	5,543 (23.8)	--	--

[a]Prior healthcare use in the 12 months prior to the last 6 months of life

[b]For people with a completed home care assessment within the last 2 years of life

COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range

3.9 Supplementary Online Content

Association Between Palliative Care and Healthcare Outcomes Among Adults Dying from Noncancer Illness

A Population-Based Matched Cohort Study

eText 3.1 - Description of datasets

All residents of Ontario have universal access to hospital care, physicians' services, and those aged ≥ 65 years of age are provided universal prescription drug insurance coverage without the requirement for co-payment. The administrative datasets used in this study were linked using encoded identifiers at the patient level and analyzed at ICES.

Description of datasets:

Database	Description
Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)	Contains detailed diagnostic and procedural information for all hospital admissions in Canada. DAD records have been demonstrated to have excellent agreement (over 99%) for demographic and administrative data. Regarding diagnoses, median agreement between original DAD records and re-abstracted records for the 50 most common most responsible diagnoses was noted to be 81% (Sensitivity 82%; Specificity 82%). The corresponding median agreement for the 50 most frequently performed surgical procedures was 92% (sensitivity 95%, positive predictive value 91%).[1]
Continuing Care Reporting System Long-Term Care (CCRS-LTC)	Contains demographic, administrative, clinical and resource utilization information on patients who receive continuing care services in hospitals or long-term care (LTC) homes in Canada. The long-term care dataset is generated from the Individual Assessment Instrument Minimum Data Set 2.0, a mandatory comprehensive, standardized and validated instrument for evaluating the needs, strengths, and preferences of elderly adults residing in nursing homes and receiving home care, contains detailed information on the functional status of these people.[2] Full assessments are completed on admission or referral, at quarterly intervals and following any significant health status change.

Home Care Database (HCD)	Contains patient-level data on government-funded home and community services.
National Ambulatory Care Reporting System (NACRS)	Reports demographic, administrative, clinical and service-specific data for Emergency Department visits.
National Rehabilitation Reporting System (NRS)	Contains patient data collected from participating adult inpatient rehabilitation facilities and programs across Canada
Ontario Congestive Heart Failure (CHF)	Contains all Ontario individuals with CHF identified since 1991. A diagnosis of HF was identified by the presence of one hospital record or physician claim, followed by a second record from either source within 1 year. This method has been previously validated with a sensitivity of 84.8% and a specificity of 97.0%.[3]
Ontario Drug Benefit (ODB)	Provides individual prescription records including all prescriptions dispensed to Ontario residents aged 65 years and older. Each medication claim has an associated prescriber identifier which indicates the health practitioner who wrote the prescription. An audit of 5,155 randomly selected prescriptions dispensed from 50 Ontario pharmacies determined that the ODB had an error rate of 0.7% and none of the pharmacy characteristics examined (locations, owner affiliation, productivity) were associated with coding errors.[4]
Ontario Health Insurance Plan (OHIP)	Identifies physician billing claims and specialty on all services provided by fee-for-service physicians in Ontario.
Ontario Mental Health Reporting System (OMHRS)	Documents data on patients in adult designated inpatient mental

	health beds. This includes beds in General, Provincial Psychiatric, and Specialty Psychiatric facilities.
Office of the Registrar General – Deaths (ORGD)	An annual dataset containing information on all deaths registered in Ontario starting on January 1 1990 that includes the cause of death as indicated on their death certificate.
Registered Persons Database (RPDB)	Registry of all Ontarians eligible to receive insured health services in the province and contains detailed demographic information as well as the Local Health Integration Networks (LHIN), which defines Ontario 14 regional areas within which people received most of their hospital care from local hospitals. The RPDB also provides information on the date and location of death for all individuals in Ontario.
Same Day Surgery (SDS)	Contains patient-level data for day surgery institutions in Ontario. Every record corresponds to one same-day surgery or procedure stay

eText 3.2 – The hospital risk score and determining functional decline in people who have received a home care assessment

The hospital frailty risk score (range 0-50) is a comprehensive and validated measure of a person's function and comorbidity that reflects global illness severity and identifies a group of patients who are at greater risk of adverse outcomes including hospitalization and 30-day mortality.[5] We categorized hospital frailty measures into 4 groups based on the distribution of scores within our cohort: 0, 0.1-8.9, ≥9 and not hospitalized.

Functional decline:

'Yes' for <u>any</u> of the following conditions:

Use a 2-year lookback from index date to determine if an person has had a prior RAI completed

a. New RAIHC assessment in the 1 year prior to *index date*
b. Increase in 1 point on activities of daily living scale (long form) from last assessment
    i. *Must fall in the 1 year prior to index date*
c. Increase in 1 point on activities of daily living scale (self-form) from last assessment
    i. *Must fall in the 1 year prior to index date*
d. Variable "ADL Decline" = "Yes" from last assessment
    i. *Must fall in the 1 year prior to index date*

If any of 'c'-'e' do not fall in the 1 year prior to index date, code this as "No" (i.e. this does not count as the presence of functional decline)

eText 3.3 - Physician claims fee codes used to identify delivery of palliative care including location

Outpatient

- A945 (without and with B codes): Special palliative care consultation in clinic, office, home; minimum 50 min
- K015 (if no other feecode combination below was met): Counselling of relatives on behalf of catastrophically or terminally ill patient
- K023 (if no other feecode combination below was met): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit. Exclude if patient is in hospital, long-term care (LTC), complex continuing care (CCC), or rehabilitation

Home-based

- A900 with (B966, B998, B997): Complex house call assessment
- A901 with (B966, B998, B997): House call assessment
- A945 with any B code: Special palliative care consultation
- K023 with A900 A901 or any B code: Palliative care support
- K015 with A900 A901 or any B code: Counselling of relatives on behalf of catastrophically or terminally ill patient
- B966: Palliative care home visit; travel premium – weekdays daytime
- B998 : Palliative care home visit; special visit premium – weekdays daytime, first person seen
- B997: Palliative care home visit; special visit premium – nights, first person seen
- A900 A901 B960 B961 B962 B963 B964 B986 B987 B988 B990 B992 B993 B994 B996 within the last 3 months prior to death

Hospital inpatient

- C945: Special palliative care consultation
- C882: Palliative care; Non-emergency subsequent visits by the MRP following transfer from an Intensive Care Area
- C982: Palliative care; Emergency subsequent visits by the MRP following transfer from an Intensive Care Area
- K015 with (C945 C882 C982): Counselling of relatives on behalf of catastrophically or terminally ill patient
- K023 with (C945 C882 C982): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit.

Subacute care

- W882: Palliative care; Long-term care subsequent visit
- W982: Palliative care; Long-term care subsequent visit (for community medicine practitioners)
- K015 with (W882 W982): Counselling of relatives on behalf of catastrophically or terminally ill patient
- K023 with (W882 W982): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit.

Third-party encounters

- G511: Telephone services to patient receiving PC at home (max. 2/week)
- G512: Weekly care case management from palliative primary care management (Monday–Sunday)
- K700: Palliative care outpatient case conference

eText 3.4 - Determining location of death using RPDB

Hospital

- Hospital
- ICU

Home

- Community
- LTC

Other

- Unknown

eText 3.5 - Capturing delivery of potentially burdensome interventions

The following Canadian Classification of Health Interventions (CCI) or OHIP service codes were used to capture the delivery of potentially burdensome interventions:

Positive pressure ventilation

- PPV 1.GZ.31

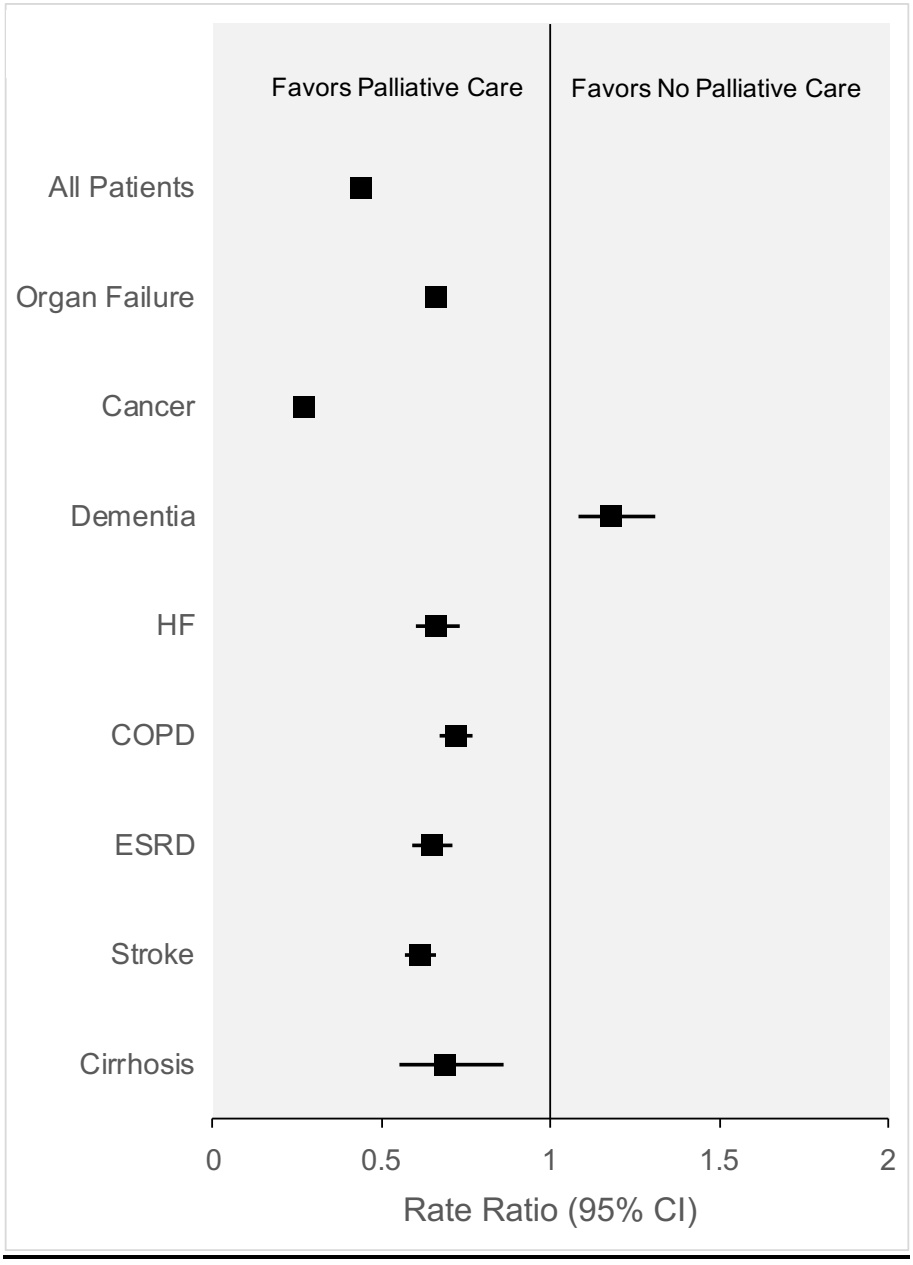
Resuscitation

- Resuscitation 1.HZ.30
- Defibrillation 1.HZ.09
- General Resuscitation G521, G522, G523

Dialysis

- 1.PZ.21

eFigure 3.1 - The association between palliative care and potentially burdensome interventions. Association between newly initiated palliative care and rates of potentially burdensome interventions (positive pressure ventilation, resuscitation, initiation of dialysis) among adults in the last 6 months of life dying from cancer and noncancer illness in Ontario between 2010 and 2015. Models were adjusted for age, sex, comorbidities, rurality, neighborhood income, frailty and hospitalizations in the year prior to index date.



eTable 3.1 – Baseline characteristics *at 6 months prior to death* of matched patients in the last 6 months of life who died of cancer in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 24,994)	**No (n = 25,226)**	**Weighted Standardized Difference**
Age in years, mean (SD)	74.5 (13.3)	75.0 (12.5)	0.03
Female sex, n (%)	12,244 (49.0)	11,267 (44.7)	0.09
Cause of death, n (%)			
Cancer	24,994 (100.0)	25,226 (100.0)	0.00
Year of death, n (%)			
2010	4,006 (16.0)	5,550 (22.0)	0.15
2011	4,162 (16.7)	5,184 (20.6)	0.10
2012	4,083 (16.3)	4,910 (19.5)	0.08
2013	4,136 (16.5)	3,414 (13.5)	0.08
2014	4,314 (17.3)	3,133 (12.4)	0.14
2015	4,293 (17.2)	3,035 (12.0)	0.15
Rural, n (%)	3,998 (16.0)	5,048 (20.0)	0.10
Hospital Frailty Score, n (%)			
Mean (SD)	4.3 (5.8)	4.6 (6.2)	0.04
Median (IQR)	2 (0-6)	2 (0-7)	0.04
0	6,308 (25.2)	6,323 (25.1)	0.00
0.1-8.9	9,522 (38.1)	9,594 (38.0)	0.00
9+	3,515 (14.1)	3,631 (14.4)	0.00
Not hospitalized	5,649 (22.6)	5,678 (22.5)	0.00
Chronic Conditions			
Arrhythmia	2,707 (10.8)	2,926 (11.6)	0.02
Cancer			
Primary	6,991 (28.0)	5,929 (23.5)	0.10
Metastatic	2,362 (9.5)	2,377 (9.4)	0.00
COPD	2,329 (9.3)	2,808 (11.1)	0.06
Congestive heart failure	1,745 (7.0)	2,031 (8.1)	0.04
Coronary artery disease	2,803 (11.2)	2,864 (11.4)	0.00
Dementia	820 (3.3)	1,444 (5.7)	0.11

Diabetes	4,203 (16.8)	4,537 (18.0)	0.03
Hypertension	17,289 (69.2)	17,635 (69.9)	0.01
Renal disease	1,089 (4.4)	1,242 (4.9)	0.02
Rheumatoid arthritis	620 (2.5)	673 (2.7)	0.01
Stroke	1,128 (4.5)	1,293 (5.1)	0.03
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	9 (0-16)	9 (1-16)	0.06
Emergency department visits	1 (0-2)	0 (0-2)	0.04
Hospitalizations	0 (0-1)	0 (0-1)	0.06

COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range

eTable 3.2 - Baseline characteristics *at date of first palliative care visit (index date)* of matched patients in the last 6 months of life who died of cancer in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 24,994)	**No (n = 25,226)**	**Weighted Standardized Difference**
Age in years, mean (SD)	74.8 (13.3)	75.3 (12.5)	0.03
Female sex, n (%)	12,244 (49.0)	11,267 (44.7)	0.09
Cause of death, n (%)			
Cancer	24,994 (100.0)	25,226 (100.0)	0.00
Year of death, n (%)			
2010	4,006 (16.0)	5,550 (22.0)	0.15
2011	4,162 (16.7)	5,184 (20.6)	0.10
2012	4,083 (16.3)	4,910 (19.5)	0.08
2013	4,136 (16.5)	3,414 (13.5)	0.08
2014	4,314 (17.3)	3,133 (12.4)	0.14
2015	4,293 (17.2)	3,035 (12.0)	0.15
Rural, n (%)	4,003 (16.0)	5,025 (19.9)	0.10
Hospital Frailty Score, n (%)	5.7 (6.5)	5.5 (6.7)	0.12
Mean (SD)	3 (0-9)	3 (0-8)	0.12

Median (IQR)	5,283 (21.1)	5,559 (22.0)	0.03
0	12,470 (49.9)	10,780 (42.7)	0.14
0.1-8.9	5,678 (22.7)	4,887 (19.4)	0.09
9+	1,563 (6.3)	4,000 (15.9)	0.31
Not hospitalized	5.7 (6.5)	5.5 (6.7)	0.12
Chronic Conditions			
Arrhythmia	3,707 (14.8)	3,609 (14.3)	0.02
Cancer			
Primary	9,010 (36.0)	7,649 (30.3)	0.12
Metastatic	9,954 (39.8)	4,437 (17.6)	0.51
COPD	3,411 (13.6)	3,385 (13.4)	0.01
Congestive heart failure	2,387 (9.6)	2,535 (10.0)	0.01
Coronary artery disease	3,254 (13.0)	3,168 (12.6)	0.01
Dementia	1,397 (5.6)	1,815 (7.2)	0.06
Diabetes	5,526 (22.1)	5,187 (20.6)	0.05
Hypertension	17,696 (70.8)	17,870 (70.8)	0.00
Renal disease	1,576 (6.3)	1,556 (6.2)	0.01
Rheumatoid arthritis	632 (2.5)	682 (2.7)	0.01
Stroke	1,567 (6.3)	1,502 (6.0)	0.01
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	12 (2-19)	11 (2-19)	0.04
Emergency department visits	2 (1-3)	1 (0-2)	0.28
Hospitalizations	1 (0-2)	0 (0-1)	0.39
Functional Decline[b]	5,397 (21.6)	4,411 (17.5)	0.11
Physician Type n,(%)			
General Practitioner	18,330 (73.3)	--	--
Specialist	6,664 (26.7)	--	--
Palliative Care Specialist	10,330 (41.3)	--	--

[a]Prior healthcare use in the 12 months prior to the last 6 months of life
[b]For people with a completed home care assessment within the last 2 years of life
COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range

eTable 3.3 – Baseline characteristics of unmatched patients in the last 6 months of life who died of noncancer illness in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 23,265)	**No (n = 40,055)**	**Standardized Difference**
Age in years, mean (SD)	84.1 (9.3)	82.7 (11.0)	0.14
Female sex, n (%)	14,153 (58.8)	33,607 (58.5)	0.01
Cause of death, n (%)			
COPD	4,155 (17.3)	11,429 (19.9)	0.07
Dementia	9,447 (39.3)	23,371 (40.7)	0.03
Cirrhosis	425 (1.8)	1,277 (2.2)	0.03
ESRD	2,492 (10.4)	4,462 (7.8)	0.09
Congestive heart failure	2,974 (12.4)	5,204 (9.1)	0.11
Stroke	4,575 (19.0)	11,735 (20.4)	0.04
Rural, n (%)	2,477 (10.3)	9,427 (16.4)	0.18
Hospital Frailty Score, n (%)			
Mean (SD)	8.8 (8.5)	8.5 (8.2)	0.03
Median (IQR)	7 (2-13)	6 (2-13)	0.03
0	2,932 (12.2)	7,100 (12.4)	0.01
0.1-8.9	8,697 (36.1)	19,625 (34.1)	0.04
9+	7,694 (32.0)	17,049 (29.7)	0.05
Not hospitalized	4,745 (19.7)	13,704 (23.8)	0.1
Chronic Conditions			

Arrhythmia	5,410 (22.5)	10,402 (18.1)	0.11
Cancer			
Primary	1,529 (6.4)	2,906 (5.1)	0.06
Metastatic	266 (1.1)	367 (0.6)	0.05
COPD	4,754 (19.8)	10,531 (18.3)	0.04
Congestive heart failure	4,871 (20.2)	9,363 (16.3)	0.1
Coronary artery disease	4,086 (17.0)	8,165 (14.2)	0.08
Dementia	4,960 (20.6)	12,905 (22.5)	0.04
Diabetes	5,113 (21.2)	11,308 (19.7)	0.04
Hypertension	20,075 (83.4)	45,454 (79.1)	0.11
Renal disease	2,747 (11.4)	4,937 (8.6)	0.09
Rheumatoid arthritis	823 (3.4)	1,659 (2.9)	0.03
Stroke	2,649 (11.0)	5,494 (9.6)	0.05
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	15 (9-21)	14 (8-21)	0.07
Emergency department visits	1 (0-2)	0 (0-2)	0.19
Hospitalizations	0 (0-1)	0 (0-1)	0.17

COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range
[a]Prior healthcare use in the 12 months prior to the last 6 months of life

eTable 3.4 – Baseline characteristics of unmatched patients in the last 6 months of life who died of cancer in Ontario between 2010 and 2015 by receipt of palliative care.

	Received Palliative Care		
	Yes (n = 23,265)	**No (n = 40,055)**	**Standardized Difference**
Age in years, mean (SD)	72.4 (12.8)	75.0 (12.6)	0.21
Female sex, n (%)	39,551 (48.2)	11,304 (44.7)	0.07
Cause of death, n (%)			
Cancer	82,120 (100.0)	25,281 (100.0)	0.00
Rural, n (%)	11,583 (14.1)	5,056 (20.0)	0.16
Hospital Frailty Score, n (%)			
Mean (SD)	3.3 (5.0)	4.6 (6.2)	0.23
Median (IQR)	1 (0-5)	2 (0-7)	0.20
0	25,458 (31.0)	6,329 (25.0)	0.13
0.1-8.9	32,893 (40.1)	9,608 (38.0)	0.04
9+	7,617 (9.3)	3,647 (14.4)	0.16
Not hospitalized	16,152 (19.7)	5,697 (22.5)	0.07
Chronic Conditions			
Arrhythmia	7,743 (9.4)	2,932 (11.6)	0.07
Cancer			
Primary	21,150 (25.8)	5,937 (23.5)	0.05
Metastatic	15,016 (18.3)	2,391 (9.5)	0.26
COPD	6,971 (8.5)	2,810 (11.1)	0.09

Congestive heart failure	4,552 (5.5)	2,034 (8.0)	0.10
Coronary artery disease	8,340 (10.2)	2,867 (11.3)	0.04
Dementia	1,829 (2.2)	1,448 (5.7)	0.18
Diabetes	14,257 (16.8)	4,539 (17.9)	0.06
Hypertension	54,605 (66.5)	17,667 (69.9)	0.07
Renal disease	2,924 (3.6)	1,244 (4.9)	0.07
Rheumatoid arthritis	1,984 (2.4)	674 (2.7)	0.02
Stroke	3,211 (3.9)	1,296 (5.1)	0.06
Prior healthcare use[a], median (IQR)			
No. unique prescription medications	8 (0-15)	9 (1-16)	0.12
Emergency department visits	1 (0-2)	0 (0-2)	0.08
Hospitalizations	0 (0-1)	0 (0-1)	0.09

COPD – Chronic obstructive pulmonary disease; ESRD – End-stage renal disease; IQR – Interquartile range
[a]Prior healthcare use in the 12 months prior to the last 6 months of life

eTable 3.5 – Healthcare use and location of death in matched patients in the last 6 months of life who died of noncancer illness in Ontario between 2010 and 2015 following initiation of palliative care or matching index date.

	Received Palliative Care	
	Yes (n = 23,265)	**No (n = 40,055)**
Emergency department visits[a]		
Cumulative number per person, mean (SD)	0.2 (0.6)	0.2 (0.6)
Cumulative number per person, median (IQR)	0 (0-0)	0 (0-0)

Rate (per person-year), median, (IQR)	0 (0-0)	0 (0-0)
Hospitalization		
Cumulative number per person, mean (SD)	0.5 (0.8)	0.5 (0.7)
Cumulative number per person, median (IQR)	0 (0-1)	0 (0-1)
Rate (per person-year), median (IQR)	0 (0-7)	0 (0-8)
ICU admissions		
Cumulative number per person, mean (SD)	0.1 (0.4)	0.1 (0.4)
Cumulative number per person, median (IQR)	0 (0-0)	0 (0-0)
Rate (per person-year), median (IQR)	0 (0-0)	0 (0-0)
Location of death, n (%)		
Hospital	5,460 (23.5)	10,632 (26.5)
ICU	684 (2.9)	3,223 (8.0)
Home	10,688 (45.9)	21,344 (53.3)
Nursing Home	2,925 (12.6)	1,566 (3.9)
Other	3,508 (15.1)	3,290 (8.2)
Active interventions[b], mean rate (SD) (person-year)	2.4 (9.7)	4.0 (12.9)

[a]Emergency department visits not resulting in hospital admission
[b]Active interventions include a composite of positive pressure ventilation, resuscitation and newly initiated dialysis
IQR – Interquartile range, SD – Standard deviation

eTable 3.6 – Healthcare use and location of death in matched patients in the last 6 months of life who died of cancer in Ontario between 2010 and 2015 following initiation of palliative care or matching index date.

	Received Palliative Care	
	Yes (n = 24,994)	**No (n = 25,226)**
Emergency department visits[a]		
Cumulative number, mean (SD)	0.4 (1.0)	0.5 (1.1)
Cumulative number, median (IQR)	0 (0-1)	0 (0-1)
Rate (per person-year), median, (IQR)	0 (0-2)	0 (0-3)
Hospitalization		

Cumulative number, mean (SD)	0.7 (0.9)	0.8 (0.8)
Cumulative number, median (IQR)	1 (0-1)	1 (0-1)
Rate (per person-year), median (IQR)	2 (0-8)	4 (0-10)
ICU admissions		
Cumulative number, mean (SD)	0.1 (0.3)	0.2 (0.5)
Cumulative number, median (IQR)	0 (0-0)	0 (0-0)
Rate (per person-year), median (IQR)	0 (0-0)	0 (0-0)
Location of death, n (%)		
Hospital	6,676 (26.7)	10,155 (40.3)
ICU	418 (1.7)	3,378 (13.4)
Home	10,184 (40.7)	7,960 (31.6)
Nursing Home	4,876 (19.5)	1,356 (5.4)
Other	2,840 (11.3)	2,377 (9.4)
Active interventions[b], mean rate (SD) (person-year)	1.0 (5.4)	3.9 (11.6)

[a]Emergency department visits not resulting in hospital admission
[b]Active interventions include a composite of positive pressure ventilation, resuscitation and newly initiated dialysis
IQR – Interquartile range, SD – Standard deviation

eTable 3.7 – Healthcare use and location of death in matched patients in the last 6 months of life who died from dementia and reside in a nursing home in Ontario between 2010 and 2015 following initiation of palliative care or matching index date.

	Unadjusted Odds Ratio (95% confidence interval)	**Adjusted[a] Odds Ratio (95% confidence interval)**
Emergency department visit[b]	0.93 (0.84-1.03)	0.83 (0.77-0.90)
Hospitalization	1.37 (1.27-1.47)	1.09 (1.01-1.08)
Death at home (versus hospital)[c]	0.66 (0.60-0.73)	0.90 (0.81-0.99)

[a]Models were adjusted for age, sex, comorbidities, rurality, neighborhood income, frailty and hospitalizations in prior year
[b]Emergency department visits not resulting in hospital admission
[c]Locations of death include home (including nursing home deaths), acute care (including hospital and ICU deaths), subacute care (including rehabilitation hospitals) and unknown.

eTable 3.8 – Healthcare use and location of death in matched patients in the last 6 months of life who died from dementia and did not reside in a nursing home in Ontario between 2010 and 2015 following initiation of palliative care or matching index date.

	Unadjusted Odds Ratio (95% confidence interval)	Adjusted[a] Odds Ratio (95% confidence interval)
Emergency department visit[b]	1.13 (1.06-1.21)	1.06 (1.01-1.12)
Hospitalization	1.53 (1.46-1.60)	1.33 (1.27-1.39)
Death at home (versus hospital)[c]	0.66 (0.60-0.73)	0.91 (0.83-1.00)

[a]Models were adjusted for age, sex, comorbidities, rurality, neighborhood income, frailty and hospitalizations in prior year
[b]Emergency department visits not resulting in hospital admission
[c]Locations of death include home (including nursing home deaths), acute care (including hospital and ICU deaths), subacute care (including rehabilitation hospitals) and unknown.

eTable 3.9 – Evaluation of effect modification by cause of death on associated healthcare use and location of death in matched patients in the last 6 months of life who died in Ontario between 2010 and 2015 following initiation of palliative care or matching index date.

	Adjusted[a] Rate or Odds Ratio (95% CI)
Emergency department visit[b]	
Reference: Organ Failure	0.88 (0.85-0.92)
Reference: Dementia	0.70 (0.67-0.74)
Reference: Cancer	0.98 (0.95-1.00)
Hospitalization	
Reference: Organ Failure	1.01 (0.99-1.04)
Reference: Dementia	0.81 (0.79-0.85)
Reference: Cancer	0.84 (0.82-0.85)
ICU Admission	
Reference: Organ Failure	0.78 (0.74-0.82)
Reference: Dementia	0.25 (0.22-0.29)
Reference: Cancer	0.20 (0.19-0.21)
Death at home (versus hospital)[c]	
Reference: Organ Failure	1.32 (1.27-1.37)
Reference: Dementia	1.58 (1.51-1.66)
Reference: Cancer	2.47 (3.39-2.55)

[a]Models were adjusted for age, sex, comorbidities, rurality, neighborhood income, frailty and hospitalizations in prior year
[b]Emergency department visits not resulting in hospital admission
[c]Locations of death include home (including nursing home deaths), acute care (including hospital and ICU deaths), subacute care (including rehabilitation hospitals) and unknown.

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4 Study #3 - Association Between Attending Physicians' Rates of Referral to Palliative Care and Location of Death in Hospitalized Adults with Serious Illness: A Population-Based Cohort Study

4.2 Key Points

Question: Are hospitalized patients who are cared for physicians with a high rate, compare to physicians with an average and low rate of referral to palliative care, less likely to die in hospital?

Findings: This population-based decedent cohort study of 7,866 physicians paired with 130,862 hospitalized adults in their last year of life who died of serious illness found that hospitalized patients cared for by a physician who referred to palliative care at a high rate had lower risk of dying in hospital than at home compared to patients who were cared for by a physician with an average rate of referral (number needed to treat (NNT) = 57 (IQR 41-92)) or by a physician with a low rate of referral (NNT = 28 patients (IQR 23-44)).

Meaning: An physicians' rate of referral to palliative care is associated with a lower risk of dying in hospital. Therefore, patients who are cared for by physicians with higher rates of referral to palliative care are less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation as a barrier to access.

4.3 Abstract

Background: Patients who receive palliative care are less likely to die in hospital.

Objective: To measure the association between physician rates of referral to palliative care and location of death in hospitalized adults with serious illness.

Research Design: Population-based decedent cohort study using linked health administrative data in Ontario, Canada.

Subjects: 7,866 physicians paired with 130,862 hospitalized adults in their last year of life who died of serious illness between 2010 and 2016.

Exposure: Physician annual rate of referral to palliative care (high, average, low).

Measures: Odds of death in hospital versus home, adjusted for patient characteristics.

Results: There was nearly 4-fold variation in the proportion of patients receiving palliative care during follow-up based on attending physician referral rates: high 42.4% (n=24,433), average 24.7% (n=10,772), low 10.7% (n=6,721). Referral to palliative care was also associated with being referred by palliative care specialists and in urban teaching hospitals. The proportion of patients who died in hospital according to physician referral rate were 47.7% (high), 50.1% (average), and 52.8% (low). Hospitalized patients cared for by a physician who referred to palliative care at a high rate had lower risk of dying in hospital than at home compared to patients who were referred by a physician with an average rate of referral (adjusted odds ratio 0.91 (95% CI 0.86 to 0.95); number needed to treat (NNT) = 57 (IQR 41 to 92)) and by a physician with a low rate of referral (adjusted odds ratio 0.81 (95% CI 0.77 to 0.84); NNT = 28 patients (IQR 23 to 44)).

Conclusions and Relevance: An attending physicians' rates of referral to palliative care is associated with a lower risk of dying in hospital. Therefore, patients who are cared for by physicians with higher rates of referral to palliative care are less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation as a barrier to access.

4.4 Introduction

Hospitalization near the end of life is common. Nearly 75% of people are hospitalized in their last year of life and 53% in the last 30 days.[11,56] High healthcare use is both costly and associated with poor quality of life.[3,8–11,15,132,133] Hospitalization itself may be used to trigger important conversations about future care planning including preferred location of death.[155] Yet many people continue to die in hospital, despite a reported preference by up to 87% of people to die at home.[44,51,67]

Palliative care primarily focuses on improving quality of life and treatment of burdensome symptoms in people with serious illness.[156] It is also associated with lower healthcare use, costs and a lower risk of dying in hospital.[45,46,66,68,157] Unfortunately, a substantial number of patients do not receive palliative care as they approach the end of life.[65]

Prior studies have reported that physician factors – in addition to patient, family, illness, and health system factors – affect the use of palliative care. This is in part due to the fact that access to palliative care requires a physician referral, and because large variation exists among physicians' referral rates to palliative care.[158–164] One important physician-level barrier may be their tendency to refer to palliative care. As hospitalized patients are randomly assigned the admitting physician who so happens to be on service (instead of choosing them), the patient's ability to access palliative care is partially controlled by their treating physician. However, it is unknown if access to palliative care through a physician's referral and other factors related to practice settings, influence the risk of dying in hospital. This study is novel because it quantifies the magnitude of the associated impact of physician referral to palliative care on the risk

of dying in hospital. Where prior studies have identified an association between receipt of palliative care overall and the risk of dying in hospital, there is limited understanding of the physician factors that contribute to it. A better understanding of how physician referral rates to palliative care impact its delivery and important outcomes such as location of death may help to inform the design of interventions that aim to reduce variation through standardization of the referral process by automatically ‘triggering’ referral of patients with serious illness to palliative care.

The objective of this study was to measure the association between a physician’s annual rate of referral to palliative care and the location of death in hospitalized adults with serious illness for whom they care.

4.5 Methods

Study Design, Setting and Data Sources

We used health administrative databases at ICES (formerly the Institute for Clinical Evaluative Sciences) to conduct a population-based cohort study in Ontario, Canada. Ontario is Canada's most populous province with nearly 14 million residents. Universal access to hospital care and medically necessary physicians' services are provided to all residents of Ontario, and those aged ≥ 65 years are provided universal prescription drug insurance coverage. We used unique patient identifiers to linked to separate Ontario administrative files , which have been used in prior studies involving palliative care (eText 4.1).[45,46,65,139] Ethics approval was obtained from Sinai Health System's research ethics board (ID 18-0015-E).

Study Cohort

Our decedent cohort included all Ontario adults (age ≥18 years) in their last year of life who died from cancer or select common and terminal noncancer causes and were hospitalized between January 1st, 2010 and December 31st, 2016. This represented approximately 30% of all deaths in Ontario. Cause of death was determined according to the ICD-10 code on their death certificate. Noncancer illness was defined as death due to heart failure (HF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), cirrhosis, stroke, dementia or hip fracture, as these diseases represent the most common terminal noncancer conditions and some are also the most well-studied in the palliative care literature.[45,66,68] For secondary analyses, we further subdivided those who died of noncancer illness into those dying of organ failure (HF,

COPD, ESRD, cirrhosis and stroke, excluding hip fracture) or dementia, which have unique trajectories of functional decline at the end of life, have different rates of referral to palliative care and may influence a person's healthcare needs and subsequent use.[80,81]

We excluded patients who did not have any inpatient physician fee claims during their hospitalization (some physicians are remunerated using payment models that do not use any fee claims), whose hospital length of stay was greater than 1 year, and those who were not Ontario residents. We excluded patients who were referred to inpatient palliative care before they were seen by their most responsible physician because these referrals are independent of their most responsible physician's referral rate to palliative care and would confound the association with our study outcomes. We also excluded patients who died on the index date because their physician would not have the opportunity to refer them to palliative care. Finally, we excluded patients paired with a physician whose specialty does not typically provide care to inpatients as an attending physician (e.g. radiology) and those who engaged in limited clinical care.[165]

Identifying a Patient's Most Responsible Physician

We paired hospitalized patients with the inpatient physician who was most responsible for their patient's care during the first hospitalization in their last year of life. In Ontario, hospitalized patients do not directly choose their inpatient physician; rather they are randomly assigned to the physician who is working that day. We intentionally chose the first hospitalization because current recommendations are to refer to palliative care earlier in the course of a patient's illness, instead of at the end of life, and early

referral to palliative care is associated with lower acute healthcare use.[47,166,167] A financial incentive in the form of a fee premium (fee code E083) is claimed by physicians who provide inpatient services as an attending physician for each day they provide care. We defined a patient's most responsible physician as the one who claimed the highest number of E083 fee codes (i.e. was the most responsible physician for the most days) among all physicians providing care to that patient during the entire hospitalization. To identify the most responsible physician in settings where physicians do not use fee-for service models (and therefore cannot use the E083 fee code), patients were paired with the physician who had the highest number of inpatient claims for that patient during their hospitalization.

Attending Physician Referral Rate to Palliative Care

The index study date was the date of first inpatient service by a patient's most responsible physician. The main exposure was the physicians' annual number of paired hospitalized patients referred to palliative care (numerator) among all hospitalized study patients for whom they provided care in that year (denominator). We identified the delivery of palliative care based on a unique set of widely used physician claims fee codes (eText 4.2).[11,46–48,65,133,136,138–140] These codes were created to specifically indicate the delivery of palliative care by all physicians. A patient was considered to be referred to palliative care if an inpatient palliative care fee code was claimed by a different physician anytime during the patient's hospitalization after the index date; or an outpatient palliative care fee code was claimed by a different physician between the index date and 14 days of discharge from hospital. We used a data-driven approach to

define categories of physician referral rates. These cut-offs were created according to the tertiles of physician referral rates among all physicians during the entire study period. We categorized an attending physician's annual rate of referral to palliative care as "low" (<20% per year), "average" (20-30% per year) and "high" (>30% per year).

Patient Characteristics

We measured demographic and clinical variables including age, sex, socioeconomic status, rural location of residence, comorbidities and chronic conditions,[141] hospital frailty score,[142] year of death, care at a teaching hospital, use of acute health care services in the year before the study's index date, and the timing of index physician visit relative to death. The hospital frailty score is a comprehensive measure of a person's comorbidity that reflects global illness severity and identifies patients at greater risk of adverse outcomes including hospitalization and 30-day mortality.[142] We categorized hospital frailty measures into 4 groups based on the distribution of scores within our cohort: 0, 0.1-8.9, ≥9 and not previously hospitalized.

Physician Characteristics

We measured attending physician-level characteristics, including age, sex, graduation from a Canadian versus foreign medical school, clinical specialty, number of years in practice, rural practice setting, the volume of inpatient and total physician service fee claims for each year in the study, and whether the physician was a palliative care specialist. Status as a palliative care specialist was captured using a validated method with a sensitivity of 76.0% and specificity of 97.8%.[139]

Outcomes

The primary outcome was the location of death, which included hospital or ICU, home or nursing home, or 'other', which included death in a subacute care setting, or an unknown location of death. Deaths that occurred in a dedicated palliative care unit (PCU) or hospice were categorized as 'other' because they cannot be distinguished from other subacute care beds such as those in a rehabilitation hospital.

The secondary outcomes were the rates of ED visits and the rates of hospitalization during follow-up. We also determined the proportion of patients who received palliative care, defined as ≥1 palliative care fee codes claimed by any physician during follow-up.

Statistical Analysis

The primary analysis measured the association between palliative care and death in hospital (versus home) in high compared to average, and in high compared to low, palliative care referring physicians. We used multivariable generalized estimating equations (GEE) to account for clustering of patients within physicians. The multilevel categorical outcome of location of death was modelled using a multinomial logistic GEE model (death in hospital/ICU versus home/nursing home vs other). ED visit rate and hospitalization rate were modelled using Poisson GEE models with follow-up time as offset. All models were adjusted for patient-specific factors including age, sex, income quintile, rurality, comorbidities and chronic conditions, frailty group, care at a teaching hospital, use of acute health care services in the year before the study's index date, and the timing of index physician visit relative to death.

We performed 3 prespecified secondary analyses of the primary outcome examining: 1) subgroups of cause of death (cancer, noncancer, organ failure and dementia), 2) 'new-users' of palliative care (those who received<2 visits with palliative care in the year prior to the index date) and 3) effect modification by proximity to death (≤7 days versus >7 days, and ≤30 days versus >30 days) as an interaction term. A 'new-user' design is often used in pharmacoepidemiology studies and minimizes bias by restricting analysis to persons who are initiating treatment, since these people are more likely to be similar at baseline when outcome risks are likely to vary over the time someone has been on treatment.[168]

To translate our findings into a clinically meaningful measure, we calculated the number of patients needed to be treated by a high compared to average, and high compared to low rate referring physician to prevent 1 in-hospital death. We calculated the crude difference and 95% CIs for the proportion of patients who died in hospital and at home after bootstrapping paired patients 1000 times to calculate the number needed to treat (NNT) and corresponding 95% CIs.[146]

We also performed a *post hoc* analysis using β-blocker ophthalmic drops as the outcome to see if patients referred by high rate physicians had a higher odds of being prescribed one of these medications during follow-up compared with average and low rate referring physicians. We selected this medication class because we anticipated no association with attending physician referral rate to palliative care intensity due to their narrow indications for use (eText 4.4).[169]

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

4.6 Results

Baseline Characteristics of Patients and Attending Physicians

There were 7,866 physicians paired with 130,862 patients; 43,846 (33.5%) patients paired with 4,094 (52.0%) low-rate physicians, 36,554 (27.9%) patients paired with 1,411 (18.0%) average-rate physicians and 50,462 (38.6%) patients paired with 2,361 (30.0%) high-rate physicians (Figure 4.1). Patients were first seen by their attending physician (index date) a median of 90 days (interquartile range (IQR) 23 to 225) before death.

Patient characteristics were generally balanced across the exposure groups. Patients were a median age of 76 years and half were female. Physician' median age was 47 years, 31% were female and had practiced a median of 20 years (IQR 11 to 30). However, some notable differences existed. A higher proportion of patients referred by high rate physicians had cancer, lived in urban centres, were cared for in teaching hospitals and had prior engagement with palliative care (Table 4.1). A higher proportion of high rate physicians were female and were palliative care specialists (Table 4.2). Among all patients, 10.7% (n=4,670) were referred to palliative care and 4.7% (n=2,051) received palliative care from a low rate physician, 24.7% (n=9,018) were referred to and 4.8% (n=1,754) received palliative care from an average rate physician, and 42.4% (n=21,387) were referred to and 6.0% (n=3,046) received palliative care from a high rate physician.

Variation in Receipt of Palliative Care

There was a 4-fold difference in the proportion of patients receiving palliative care during follow-up who were referred by high rate physicians (42.4%) compared to average (24.7%) and low rate physicians (10.7%). Among patients receiving palliative care during follow-up, 50.3% who were referred by high rate physicians had multiple (≥2) palliative care visits, compared to 44.3% for those referred by average and 39.3% by low rate physicians.

Location of Death

Overall, 65,550 (50.1%) patients died in hospital. Among all hospitalized patients, 13.2% (n=17,195) who were referred to palliative care or received palliative care from their most responsible physician died in hospital compared to 36.9% (n=48,163) who did not receive referral to palliative care or palliative care from their physician. Patients who were referred by high rate physicians had a lower risk of dying in hospital or ICU than at home (n=24,067; (47.7%)), compared to those referred by average (n=18,320; (50.1%); adjusted odds ratio (aOR) 0.91 [95% confidence interval (CI) 0.86 to 0.95]) and low rate physicians (n=23,173 (52.8%); aOR 0.81 [95% CI 0.77 to 0.84]) (Figure 4.2, Table 4.3). The magnitude of the association was similar among those dying from cancer (high vs average aOR 0.91 [95% CI 0.85 to 0.96]; high versus low aOR 0.76 [95% CI 0.72 to 0.80]) compared to chronic organ failure (high vs average aOR 0.90 [95% CI 0.86 to 0.95]; high versus low aOR 0.78 [95% CI 0.75 to 0.82]) (Figure 4.2). No association was observed when comparing location of death in patients dying of dementia referred by high compared to average rate physicians (aOR 1.01 [95% CI 0.91 to 1.13]) or high compared to low rate physicians (aOR 1.10 [95% CI 0.98 to 1.23])

(Figure 4.2). The magnitude of the association was similar among new users of palliative care (eTable 4.1).

There was 1 fewer associated hospital death for every 57 (IQR 41 to 92) patients referred by a physician who had a high rate of referral to palliative care compared to patients referred by a physician with an average rate of referral. There was 1 fewer associated hospital death for every 28 patients (IQR 23 to 44) referred by a physician who had a high rate of referral to palliative care compared to patients who were referred by a physician with a low rate of referral.

Patients who were ≤30 days from death and referred by high rate physicians had a lower odds of dying in hospital or ICU than at home, compared to those who were referred by average (aOR 0.71 [95% CI 0.68 to 0.75]) or low rate physicians (aOR 0.65 [95% CI 0.62 to 0.68]). Similar findings existed for patients who were ≤7 days from death (high versus average: aOR 0.77 [95% CI 0.74 to 0.81]; high versus low: aOR) 0.70 [95% CI 0.67 to 0.73]).

There was no association between attending physician referral rate to palliative care and prescription of β-blocker eye drops among patients who were referred by high compared to average rate physicians. Patients referred by high rate physicians had a higher odds of receiving β-blocker eye drops, compared to those who were referred by low rate physicians (eText 4.4).

Subsequent Acute Healthcare Use

There were 44,928 (34.3%) patients with ≥1 emergency department visit during follow-up. The median number of emergency department visits was 0 (IQR 0 to 2) per

person-year. Patients referred by high rate physicians had lower emergency department use, compared to those referred by average (adjusted rate ratio (aRR) 0.95 [95% CI 0.92 to 0.98]) or low rate physicians (aRR) 0.89 [95% CI 0.86 to 0.92]).

There were 73,003 (55.7%) patients with ≥1 hospitalization during follow-up. The median number of hospitalizations was 1 (IQR 0 to 5) per person year. There was no association between attending physician rate of referral to palliative care and hospitalization across all exposure groups (eTable 4.2).

4.7 Discussion

We found that patients cared for by attending physicians who more frequently referred their patients to palliative care services were less likely to die in hospital. Patients with cancer, who had previously engaged with palliative care, who lived in an urban centre and were cared for in teaching hospitals were more likely to be paired with a high rate physician who was also more likely to be a palliative care specialist. The observed lowered risk of dying in hospital likely reflects the combined effects of patient, physician and hospital factors related to different practice environments that emphasize particular types of care. These findings translated to 1 fewer hospital death for every 57 (IQR 41 to 92) patients cared for by physicians with a high compared to average rate of referral, and 1 fewer hospital death for every 28 (IQR 23 to 34) patients cared for by physicians with a high compared to low rate of referral.

Our study, which uses physician referral rate and an intermediary step in the receipt of palliative care, is consistent with prior work demonstrating that palliative care was associated with lower risk of dying in hospital. A home death is preferred by most people die and is considered a recognized indicator of high-quality end-of-life care.[45,51–53,66] The substantial difference in proportion of patients who received palliative care during follow-up suggests that referral to palliative care may be playing some role in achieving a home death for those who prefer it. Indeed, prior research has established a strong association between receipt of palliative care and death at home.[45,66] At the physician level, self-rated knowledge of end-of-life care differs between specialties, and a traditional focus on a curative approach may make it difficult for some physicians to transition their patients to a philosophy of care focused on quality, and not quantity, of

life.[161] A lack of clear eligibility criteria may also play a role; physicians may not recognize their patient's palliative needs and therefore not make a referral during their course of illness.[160,161,164,170–173]

Patients who were referred by a high rate physician appeared to have better outcomes. Our physician-level exposure does not suggest that referral rate is responsible for the entire effect of palliative care on location of death. Instead, it suggests that the risk of dying in hospital is attributable to any and all treatments provided to the patients in the different exposure groups. Our study points to plausible mechanisms through which higher rates of referral to palliative care may be associated with lower risk of dying in hospital. Patients with cancer, who had previously engaged with palliative care, who lived in an urban centre and were cared for in teaching hospitals were more likely to be referred by a high rate physician who was also more likely to be a palliative care specialist. Hospitalized patients in Ontario do not directly choose their inpatient physician; rather they are randomly assigned to the physician who is working that day. Therefore, proposed mechanisms involving referral rates and risk of dying in hospital are unlikely to be related to patients specifically seeking out physicians who are tightly linked to and use palliative care. The observed lowered risk of dying in hospital likely reflects the combined effects of factors related to different practice environments that emphasize particular types of care.

Limitations

Our study is limited by a lack of information on individual patient preferences for engagement with palliative care, their preferred location of death, and their ability to be

cared for at home if their health status worsened. Second, we cannot rule out the possibility of downstream co-interventions that may influence location of death as patients were referred an average of 90 days before death. Third, the generalizability of our findings to the outpatient setting and referral behaviors of physicians who provide care in that setting is unclear. Fourth, the observational design of our study limits understanding of the causal mechanism related to our findings. Referral rate may simply be a proxy for palliative care receipt. Alternatively, physicians who favour palliative care may use a less aggressive approach for their patients and focus on eliciting their preferences to guide care. We also did not account for facility- or regional-level rates of palliative care delivery in our analytic models, which may contribute to a practice environment that emphasize particular types of care. Fifth, the notable relative differences in prescription of β-blocker eyedrops between patients referred by high vs. low physician groups correspond to negligible absolute differences in the number of patients actually receiving these medications and is likely not clinically meaningful.

4.8 Conclusions

An attending physicians' rates of referral to palliative care is associated with a lower risk of dying in hospital. Therefore, patients who are cared for by physicians with higher rates of referral to palliative care are less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation as a barrier to access.

Figure 4.1 – Flow diagram for the creation of the study sample. All hospitalized adults in their last year of life who died from heart failure (HF), chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD), stroke, dementia, hip fracture or cancer were eligible for inclusion in the study. Patients were paired with the attending physician who was most responsible for their care during hospitalization and grouped according to the attending physicians rate of referral to palliative care.

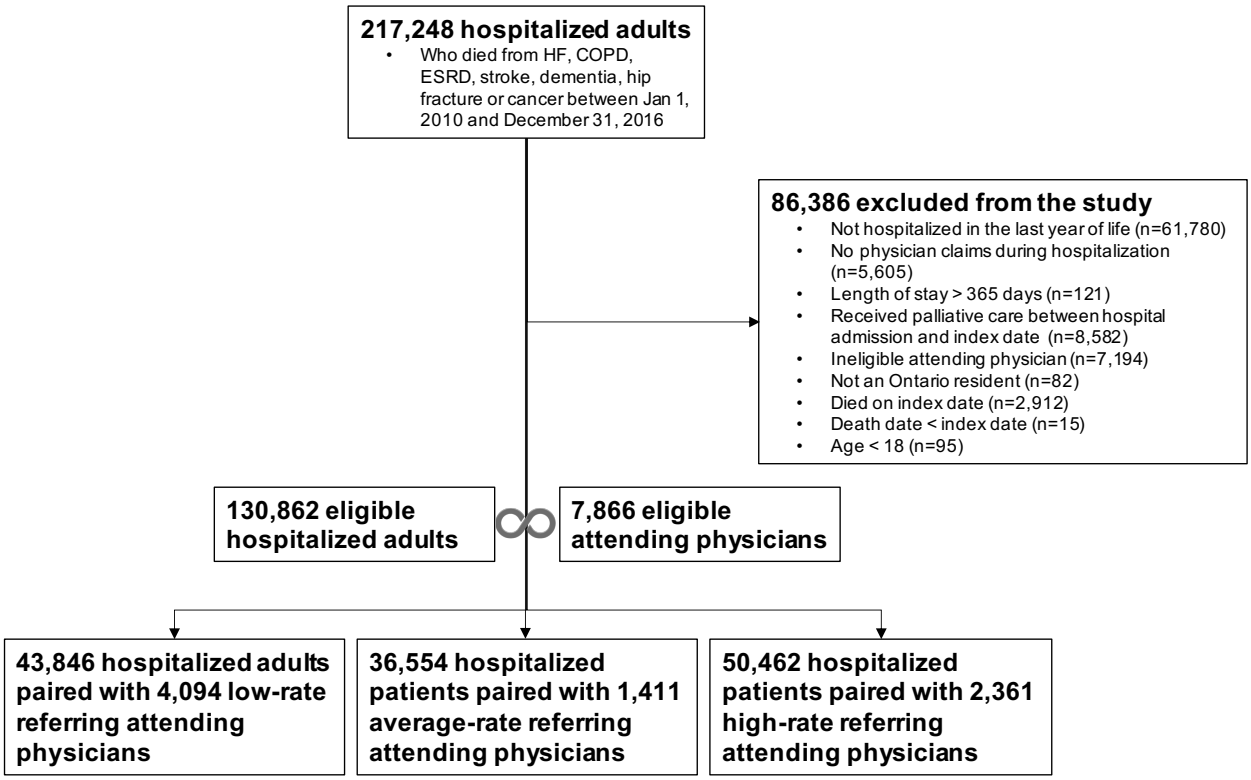

Figure 4.2 - Association Between Rates of Physician Referral to Palliative Care and Location of Death in Hospitalized Adults. Association between death at home (versus hospital) in (A) high- compared to average-rate and (B) high- compared to low-rate referring physicians among hospitalized adults in the last year of life who died of serious illness in Ontario between 2010 and 2016. Models were adjusted for age, sex, income quintile, rurality, frailty group, and metastatic cancer.

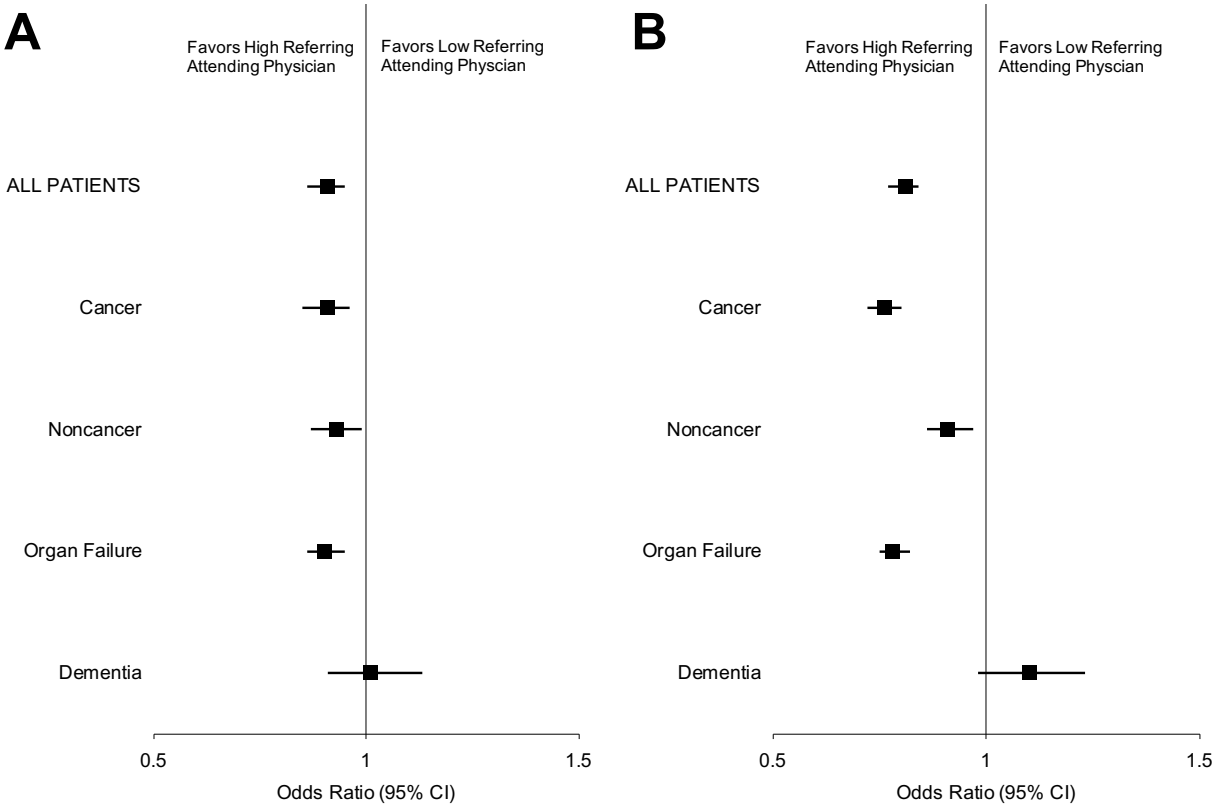

Table 4.1 – Baseline characteristics of hospitalized patients in the last year of life who died of serious illness in Ontario between 2010 and 2016 by attending physician rate of referral to palliative care.

	Attending physician rate of referral to palliative care		
	Low (<20) (N=43,846)	**Avg (20-30) (N=36,554)**	**High (>30) (N=50,462)**
Age in years, mean (SD)	77.4 (12.1)	77.2 (12.5)	75.5 (13.3)
Female sex, n (%)	21,330 (48.6%)	17,928 (49.0%)	25,689 (50.9%)
Cause of death, n (%)			
Cancer	24,215 (55.2%)	21,223 (58.1%)	34,094 (67.6%)
Noncancer	19,631 (44.8%)	15,331 (41.9%)	16,368 (32.4%)
Organ Failure	14,928 (34.1%)	11,078 (30.3%)	10,818 (21.4%)
Dementia	4,703 (10.7%)	4,253 (11.6%)	5,550 (11.0%)
Hip Fracture	67 (0.2%)	51 (0.1%)	41 (0.1%)
Rural, n (%)	10,185 (23.2%)	4,806 (13.1%)	3,436 (6.8%)
Neighbourhood Income Quintile, n (%)			
Lowest	10,862 (24.8%)	8,599 (23.5%)	11,772 (23.3%)
Low	9,619 (21.9%)	8,023 (21.9%)	11,108 (22.0%)
Middle	8,624 (19.7%)	7,254 (19.8%)	9,509 (18.8%)
High	7,809 (17.8%)	6,498 (17.8%)	9,052 (17.9%)

Highest	6,800 (15.5%)	6,050 (16.6%)	8,871 (17.6%)
Missing	132 (0.3%)	130 (0.4%)	150 (0.3%)
Hospital Frailty Score, n (%)			
Mean (SD)	7.3 (7.3)	7.6 (7.6)	7.1 (7.5)
Median (IQR)	5 (2-11)	5 (2-11)	5 (2-10)
0	5,661 (12.9%)	4,759 (13.0%)	7,527 (14.9%)
0.1-4.9	15,925 (36.3%)	12,588 (34.4%)	18,334 (36.3%)
5.0-8.9	8,617 (19.7%)	7,315 (20.0%)	9,494 (18.8%)
9+	13,643 (31.1%)	11,892 (32.5%)	15,107 (29.9%)
Received Care in Teaching Hospital	8,927 (20.4%)	9,762 (26.7%)	19,412 (38.5%)
Engagement with Palliative Care (2+ visits) in Year Prior	4,021 (9.2%)	4,119 (11.3%)	9,723 (19.3%)
Time from MRP Attending Physician Visit (index date) to Death (days), median (IQR)	110 (25-244)	92 (23-226)	76 (21-204)

MRP – Most responsible physician
IQR -Interquartile range

Table 4.2 – Baseline characteristics of attending physicians paired with hospitalized patients in the last year of life who died of serious illness in Ontario between 2010 and 2016 by attending physician rate of referral to palliative care.

	Attending physician rate of referral to palliative care		
	Low (N=4,094)	**Average (N=1,411)**	**High (N=2,361)**
Age in years, mean (SD)	48.9 (11.3)	47.7 (10.9)	45.9 (11.0)
Female sex, n (%)	1,098 (26.8%)	431 (30.5%)	935 (39.6%)
Rural, n (%)	640 (15.6%)	176 (12.5%)	155 (6.6%)
Canadian medical graduate, n (%)	2,964 (72.4%)	1,021 (72.4%)	1,615 (68.4%)
Years in practice, median (IQR)	21 (12-32)	19 (11-30)	18 (9-28)
Practice specialty, n (%)	3,189 (77.9%)	1,150 (81.5%)	1,912 (81.0%)
Medical	3,189 (77.9%)	1,150 (81.5%)	1,912 (81.0%)
Surgical	905 (22.1%)	261 (18.5%)	449 (19.0%)
Palliative Care Specialist, n (%)	61 (1.5%)	45 (3.2%)	213 (9.0%)
Attending physician delivered palliative care, n (%)	4.7%	4.8%	6.0%
Average number of paired patients per year, mean (SD)	2.3 (2.7)	4.4 (4.6)	4.1 (4.9)
Total consults per year, median (IQR)	2,941 (1,718-4,299)	3,023 (2,075-4,210)	2,494 (1,654-3,489)
Ratio of hospital to total patient visits, % (SD)	27.9% (26.2)	36.7% (28.5)	36.8% (29.9)

SD – Standard deviation; IQR – Interquartile Range

Table 4.3 – Location of death in hospitalized patients in the last year of life who died of cancer and noncancer illness in Ontario between 2010 and 2016 by attending physician rate of referral to palliative care.

	Attending physician rate of referral to palliative care		
Location of Death, n (%)	**Low (<20) (N=43,846)**	**Avg (20-30) (N=36,554)**	**High (>30) (N=50,462)**
Hospital	23,173 (52.8%)	18,320 (50.1%)	24,067 (47.7%)
Home	19,698 (44.9%)	17,374 (47.6%)	25,177 (49.9%)
Other	985 (2.2%)	860 (2.3%)	1,218 (2.4%)

4.9 Supplementary Online Content

Association Between Attending Physicians' Rates of Referral to Palliative Care and Location of Death in Hospitalized Adults with Serious Illness

A Population-Based Cohort Study

eText 4.1 - Description of datasets

All residents of Ontario have universal access to hospital care, physicians' services, and those aged ≥ 65 years of age are provided universal prescription drug insurance coverage without the requirement for co-payment. The administrative datasets used in this study were linked using encoded identifiers at the patient level and analyzed at ICES.

Description of datasets:

Database	Description
Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)	Contains detailed diagnostic and procedural information for all hospital admissions in Canada. DAD records have been demonstrated to have excellent agreement (over 99%) for demographic and administrative data. Regarding diagnoses, median agreement between original DAD records and re-abstracted records for the 50 most common most responsible diagnoses was noted to be 81% (Sensitivity 82%; Specificity 82%). The corresponding median agreement for the 50 most frequently performed surgical procedures was 92% (sensitivity 95%, positive predictive value 91%).[1]
Continuing Care Reporting System Long-Term Care (CCRS-LTC)	Contains demographic, administrative, clinical and resource utilization information on patients who receive continuing care services in hospitals or long-term care (LTC) homes in Canada. The long-term care dataset is generated from the Individual Assessment Instrument Minimum Data Set 2.0, a mandatory comprehensive, standardized and validated instrument for evaluating the needs, strengths, and preferences of elderly adults residing in nursing homes and receiving home care, contains detailed information on the functional status of these people.[2] Full assessments are completed on admission or referral, at quarterly intervals and following any significant health status change.

Home Care Database (HCD)	Contains patient-level data on government-funded home and community services.
National Ambulatory Care Reporting System (NACRS)	Reports demographic, administrative, clinical and service-specific data for Emergency Department visits.
National Rehabilitation Reporting System (NRS)	Contains patient data collected from participating adult inpatient rehabilitation facilities and programs across Canada
Ontario Congestive Heart Failure (CHF)	Contains all Ontario individuals with CHF identified since 1991. A diagnosis of HF was identified by the presence of one hospital record or physician claim, followed by a second record from either source within 1 year. This method has been previously validated with a sensitivity of 84.8% and a specificity of 97.0%.[3]
Ontario Drug Benefit (ODB)	Provides individual prescription records including all prescriptions dispensed to Ontario residents aged 65 years and older. Each medication claim has an associated prescriber identifier which indicates the health practitioner who wrote the prescription. An audit of 5,155 randomly selected prescriptions dispensed from 50 Ontario pharmacies determined that the ODB had an error rate of 0.7% and none of the pharmacy characteristics examined (locations, owner affiliation, productivity) were associated with coding errors.[4]
Ontario Health Insurance Plan (OHIP)	Identifies physician billing claims and specialty on all services provided by fee-for-service physicians in Ontario.
Ontario Mental Health Reporting System (OMHRS)	Documents data on patients in adult designated inpatient mental

	health beds. This includes beds in General, Provincial Psychiatric, and Specialty Psychiatric facilities.
Office of the Registrar General – Deaths (ORGD)	An annual dataset containing information on all deaths registered in Ontario starting on January 1 1990 that includes the cause of death as indicated on their death certificate.
ICES Physician Database (IPDB)	contains yearly information about all physicians in Ontario including physician demographics (gender, sex); specialty (functional and certified); location; measures of physician activity (billings, workload, types or services provided).
Registered Persons Database (RPDB)	Registry of all Ontarians eligible to receive insured health services in the province and contains detailed demographic information as well as the Local Health Integration Networks (LHIN), which defines Ontario 14 regional areas within which people received most of their hospital care from local hospitals. The RPDB also provides information on the date and location of death for all individuals in Ontario.
Same Day Surgery (SDS)	Contains patient-level data for day surgery institutions in Ontario. Every record corresponds to one same-day surgery or procedure stay

eText 4.2 - Physician claims fee codes used to identify delivery of palliative care including location

Outpatient

- A945 (without and with B codes): Special palliative care consultation in clinic, office, home; minimum 50 min
- K015 (if no other feecode combination below was met): Counselling of relatives on behalf of catastrophically or terminally ill patient

- K023 (if no other feecode combination below was met): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit. Exclude if patient is in hospital, long-term care (LTC), complex continuing care (CCC), or rehabilitation

Home-based

- A900 with (B966, B998, B997): Complex house call assessment
- A901 with (B966, B998, B997): House call assessment
- A945 with any B code: Special palliative care consultation
- K023 with A900 A901 or any B code: Palliative care support
- K015 with A900 A901 or any B code: Counselling of relatives on behalf of catastrophically or terminally ill patient
- B966: Palliative care home visit; travel premium – weekdays daytime
- B998 : Palliative care home visit; special visit premium – weekdays daytime, first person seen
- B997: Palliative care home visit; special visit premium – nights, first person seen
- A900 A901 B960 B961 B962 B963 B964 B986 B987 B988 B990 B992 B993 B994 B996 within the last 3 months prior to death

Hospital inpatient

- C945: Special palliative care consultation
- C882: Palliative care; Non-emergency subsequent visits by the MRP following transfer from an Intensive Care Area
- C982: Palliative care; Emergency subsequent visits by the MRP following transfer from an Intensive Care Area
- K015 with (C945 C882 C982): Counselling of relatives on behalf of catastrophically or terminally ill patient
- K023 with (C945 C882 C982): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit.

Subacute care

- W882: Palliative care; Long-term care subsequent visit
- W982: Palliative care; Long-term care subsequent visit (for community medicine practitioners)
- K015 with (W882 W982): Counselling of relatives on behalf of catastrophically or terminally ill patient
- K023 with (W882 W982): Palliative care support in half hour increments; may be used to add time for longer consultations following a code for A945, or for any PC support visit.

Third-party encounters

- G511: Telephone services to patient receiving PC at home (max. 2/week)
- G512: Weekly care case management from palliative primary care management (Monday–Sunday)
- K700: Palliative care outpatient case conference

eText 4.3 - Determining location of death using RPDB

Hospital
- Hospital
- ICU

Home
- Community
- LTC

Other
- Rehabilitation Institution
- Unknown

eText 4.4 – *Post hoc* analysis using β-blocker eye drops

There was no association between attending physician referral rate to palliative care and prescription of β-blocker eye drops among patients who were cared for by high (n=1,176; (2.3%)) compared to average rate referring physicians (n=890 (2.4%); aOR 0.96 [95% CI 0.87-1.05]). Patients cared for by a high rate referring physician had a higher odds of receiving β-blocker eye drops, compared to those who were cared for by low rate referring physicians (n=1,251 (2.9%); aOR 1.11 [95% CI 1.02-1.22]).

eTable 4.1 – Association between attending physician referral rate to palliative care and location of death or healthcare use in hospitalized patients who were new users of palliative care who died of serious illness in Ontario between 2010 and 2016.

	Attending Physician Referral Group	
	High versus Low	**High versus Average**
Death in Hospital (versus home)[a]		
Unadjusted	0.83 (0.79-0.86)	0.91 (0.87-0.96)
Adjusted[b]	0.84 (0.80-0.88)	0.93 (0.88-0.98)

[a]Locations of death include home (including nursing home deaths), hospital (including ICU) and other.
[b]Models were adjusted for age, sex, income quintile, rurality, comorbidities and chronic conditions, frailty group, cause of death (e.g. cancer, dementia), care at a teaching hospital, use of acute health care services in the year before the study's index date, and the timing of index physician visit relative to death.

eTable 4.2 – Association between attending physician referral rate to palliative care and healthcare use in hospitalized patients who died of serious illness in Ontario between 2010 and 2016.

	Attending Physician Referral Group	
	High versus Average	**High versus Low**
Emergency department visit[a]		
Unadjusted	0.94 (0.90-0.97)	0.82 (0.79-0.85)
Adjusted[b]	0.95 (0.92-0.98)	0.89 (0.86-0.92)
Hospitalization		
Unadjusted	1.02 (1.00-1.04)	1.03 (1.01-1.05)
Adjusted[b]	1.01 (0.99-1.03)	1.00 (0.99-1.02)

[a]Emergency department visits not resulting in hospital admission
[b]Models were adjusted for age, sex, income quintile, rurality, comorbidities and chronic conditions, frailty group, cause of death (e.g. cancer, dementia), care at a teaching hospital, use of acute health care services in the year before the study's index date, and the timing of index physician visit relative to death.

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5 Discussion

5.2 Were the thesis objectives met?

5.2.1 Study #1: Association of Receipt of Palliative Care Interventions with Healthcare Use, Quality of Life, and Symptom Burden Among Adults with Chronic Noncancer Illness: A Systematic Review and Meta-analysis

Objective: To measure the association between palliative care and acute healthcare use, quality of life (QOL) and symptom burden in adults with chronic noncancer illnesses.

Findings: This systematic review and meta-analysis of randomized clinical trials of patients with primarily noncancer illness found that palliative care, compared with usual care, was significantly associated with less acute healthcare use and modestly lower symptom burden, but there was no significant difference in quality of life. Analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit generalizability to other chronic illnesses.

5.2.2 Study #2: Association Between Palliative Care and Healthcare Outcomes Among Adults Dying from Noncancer Illness: A Population-Based Matched Cohort Study

Objective: To measure the association between newly initiated palliative care in the last 6 months of life, healthcare use and location of death in adults dying from noncancer illness; and to compare these associations with those who die from cancer at a population level.

Findings: Among those dying of noncancer illness related to chronic organ failure, physician-delivered palliative care was associated with a reduction in the rate of emergency department visits, hospitalizations and ICU admissions, respectively. Palliative care was associated with increased rates of emergency department visits and hospitalization in patients dying of dementia, which differed depending upon whether they lived in the community or in a nursing home. Palliative care was also associated with an increased odds of death at home.

5.2.3 Study #3: Association Between Attending Physicians' Rates of Referral to Palliative Care and Location of Death in Hospitalized Adults with Serious Illness: A Population-Based Cohort Study

Objective: To measure the association between physician rates of referral to palliative care and location of death in hospitalized adults with serious illness.

Findings: An attending physicians' rates of referral to palliative care is associated with a lower risk of dying in hospital. Therefore, patients who are cared for by physicians with higher rates of referral to palliative care are less likely to die in hospital and more likely to die at home. Standardizing referral to palliative care may help reduce physician-level variation as a barrier to access.

5.2.4 Conclusion

The objectives for all three studies were met.

5.3 Limitations

5.3.1 Individual preferences, perceptions of value

The lack of understanding of individual patient preferences for care at the end of life is perhaps the most significant limitation of this thesis work. We also lacked an understanding of patient's willingness to engage with palliative care, their preferred location of death, and their ability to be cared for at home if their health status worsened Administrative data in Ontario does not routinely collect patient preferences for care or preferences for location of death. In an era of increasing focus on the delivery of patient-centred, high-value care, the benefits of palliative care may be more appropriately measured in its ability to achieve the patient's expressed goals with equal attention paid to the associated costs.[59,63,174] The majority of patients prefer to be comfortable, with the ability to be cared for and die at home as their priorities for health at the end of life.[23,51,175] In regions of limited healthcare access, some patients may not be able to receive care at home and avoid potential transfers to the ED or hospital, regardless of their preferences. Still, our findings on the associated benefits of palliative care to reduce healthcare use and increase the possibility of a home death are therefore likely to align with the majority of, but not all, patient preferences. Our results demonstrating a reduction in symptom burden associated with palliative care also aligns with the priorities of most patients to remain comfortable at the end of life.

5.3.2 Confounding by indication

In palliative care research, confounding by indication is one of the largest threats to its validity. Patients with more severe illness who have higher healthcare use may be

more likely to receive palliative care. This may be related to recognition of their limited prognosis and palliative care needs by their healthcare providers and/or to more immediate access to inpatient palliative care when hospitalized. In study #2, patients who received palliative care were generally sicker than those who did not, as reflected by higher medication and healthcare use, a larger number of comorbidities and higher frailty risk scores. The effect of this confounding by indication may underestimate the magnitude of our results as these patients may be more likely to have higher future healthcare use. We used a combination of robust statistical approaches intended to minimize this risk, including: 1) matching on several factors strongly associated with exposure to palliative care; 2) the use of a cohort of patients who were in the last 6 months of life (to minimize the effects due to time-varying covariates and because baseline patient variables achieved a better balance at 6 compared to 12 months); and 3) a "new-user" design to increase the likelihood that the groups of patients would be similar at baseline. Consequently, we found only marginal differences between our unadjusted and adjusted results which reflects the presence of minimal amounts of measured confounding.

Current recommendations from several societies encourage the integration of palliative care early in the course of a person's disease, instead of at the end of life.[134,149,150] Patients with more advanced illness often received late referral to palliative care services that may limit several opportunities to relieve potentially avoidable suffering. Presently, there are no agreed upon standards outlining the optimal timing of palliative care initiation, which is also a source of ongoing debate.

5.3.3 Data accuracy (Misclassification)

The results of studies #2 and #3 may be underestimated due to misclassification bias if physicians are providing palliative care but are not using dedicated palliative care fee codes. For example, a cardiologist who engages in a thorough goals of care discussion and delivers care focused on symptom relief and improvements in quality of life is providing palliative care, which is associate with reduced healthcare use near the end of life. However, if the same cardiologist doesn't use palliative care fee codes to reimburse these services, then the "unexposed" patient will have outcomes similar to those who are exposed to palliative care and bias the results toward the null.

In other jurisdictions like the US which use different funding mechanisms such as the Medicare Hospice Benefit, palliative care may be delivered by healthcare providers other than physicians, which may include nurse practitioners or social workers.[98] Delivery of care by these providers and its association with important outcomes is not captured in our study using physician fee claims. However, the use of fee codes in administrative data as a means to capturing delivery of palliative care is a strength of our studies given that care classification has been less successful in health systems without universal coverage.[151]

We intentionally used the information on a patient's death certificate to categorize distinct types of serious illness to maximize specificity. This approach likely decreased the overall denominator in our study population. While this may result in inflated confidence intervals, we still found significant differences in many outcomes. We were especially concerned that other approaches may introduce too much heterogeneity and other sources of bias.

Finally, we assumed that patients received palliative care for issues related to their identified cause of death. In reality, many of these complex patients had multiple comorbidities, possibly including cancer, which likely contributed to their overall palliative needs. Prior work also demonstrates that patients with metastatic cancer are more likely to receive palliative care than other disease groups, even in the presence of other types of serious illness.[65,136]

5.3.4 Selection Bias and Generalizability

The use of a systematic approach to our literature search, clearly pre-defined study inclusion and exclusion criteria, independent study selection and review, as well as the use of population-level data minimized the risk of selection bias across all thesis studies.

When using multiple linked administrative datasets, the possibility of linkage error arises. This is typically related either false-matches where records from different people are erroneously linked or missed-matches where records from the same person fail to link. Common reasons for linkage error are related to variables that are prone to misreporting through typographical errors, time-varying changes or missing values. False-matches can lead to spurious associations when none truly exist. Loss of generalizability or the introduction of selection bias can occur in the case of missed-matches specifically, if certain measures are more or less likely to link.[176] To minimize this risk, all data is thoroughly inspected and cleaned as well as its completeness and quality metrics are openly reported in its data dictionary. These metrics were

incorporated into the selection of variables used within our studies to minimize this risk of bias.

Finally, our cohort studies were conducting using data from an ethnically diverse population in a high-income urbanized nation with universal healthcare coverage. The generalizability of our findings on the associated benefits of palliative care may not be applicable to low-income nations with limited resources to deliver components such as home-based palliative care, to nations with more homogenous cultural and religious beliefs, to rural regions with more limited availability of palliative care, and to jurisdictions without universal healthcare coverage.

5.3.5 Causality in Meta-Analyses

The summary estimates from a meta-analysis of randomized controlled trials without access to patient-level data is reported at the study level, instead of at the patient level. These summary estimates are therefore considered associations and not causal relationships, in contrast to individual randomized controlled trials. In other words, the overall summary effect of a meta-analysis represents the study-specific true effects, without estimating a true overall effect. This is an important distinction as there may be no population of patients or interventions for which the summary effect is true, which can limit the generalizability of its findings.

Meta-analysis should also be interpreted with special consideration of the qualitative and quantitative heterogeneity across the included studies. The use of a random-effects analytical method is beneficial as it measures heterogeneity between studies. This heterogeneity is introduced for example when patient populations and

differences in interventions (such as timing, intensity and makeup of a complex intervention like palliative care) vary across the individual studies. These differences reduce confidence that each study is actually measuring the "true" effect of the intervention. The random-effects meta-analysis does not explain heterogeneity, it simply measures it using estimates such as Tau and I^2. Generally, if I^2 exceeds 50% to 75%, the summary estimate is felt to be unrepresentative of the underlying effects and potentially obscure important differences.[90] The use of subgroups and meta-regression analyses help to reduce heterogeneity, remembering that these are limited to exploratory, hypothesis generating findings and not estimates of the true effect.

5.4 Implications for Clinical Decision-Making and Policy

The collective findings of the work presented in this thesis have substantial implications for decision-making at the patient, clinician, hospital, healthcare system and policy level. Patients are likely to increase requests for referral to palliative care as they become increasingly aware of its benefits across many disease types, especially when those benefits are likely to impact upon outcomes that are directly relevant to them such as symptom burden, quality of life and location of death. It will be important to raise awareness of its benefits and ensure equitable access to palliative care is available to make certain that all patients are at least offered the opportunity to receive high-quality end-of-life care. Developing innovative models of access, such as through virtual palliative care, may help to achieve these goals of ensuring equitable access, especially for patients in rural areas where palliative care is less readily available.

Clinicians who wish to continue practicing evidence-based medicine as part of an approach to improving the care of their patients will increasingly deliver and refer their patients to palliative care to take advantage of its benefits. Concerted efforts are required in knowledge translation beyond inclusion in clinical practice guidelines, to improve individual and groups of clinicians' competencies in delivery and referral to palliative care. The current variation in recognition, attitude toward and referral to palliative care across clinicians may warrant higher order interventions beyond education and feedback to reduce this variation through automation, standardization, and force functions. Further, clinicians may increasingly recognize the value and skillset of palliative care in having difficult conversations when faced with discordance between their professional views of what is achievable for their patient and the views of their patient or caregiver. It will be imperative that these clinicians can readily access palliative care to aid in these types of circumstances in a timely manner.

Hospitals are under increasing pressure to control costs and ovoid overcrowding that leads to undesirable "hallway medicine". As current evidence for palliative care suggests an overall reduction in acute healthcare use, it holds promise to play a role in alleviating high healthcare use for some of the most complex patients nearing the end of life. Perhaps more importantly, palliative care is a multidisciplinary "cross-jurisdictional" specialty, providing consultation and care in every setting of the hospital ecosystem. As such, there is an opportunity to integrate palliative care across its programs and help align care with the core strategic priorities of the hospital. Such a far-reaching vision for the integration of palliative care into a larger hospital system requires investment in leadership, program development and staffing at all levels. Hospitals connected with a

rich network of outpatient providers will need to develop methods to effectively communicate their patient's care plans between these potential silos of care and facilitate the organization of care delivery when transitioning in and out of hospital.

Regional and healthcare systems should leverage the ability of palliative care to facilitate transitional care from the hospital to home for patients nearing the end of life. Many palliative care programs offer the ability to provide care in the patient's home, often with the goal of dying there. Meeting the care requirements of patients dying in their home will require substantial investment in outpatient resourcing and staffing. Further, the coordination of care for these patients, many of whom may still require multiple transitions between care settings, is a challenging and resource intensive exercise. Patients are aging and becoming increasingly medically complex. It is unlikely that palliative care teams consisting of a single physician with expertise in a single specialty will be able to manage the myriad of issues facing their patients, even with the integration of other allied care professionals such as nursing, social work and spiritual care. The involvement of additional generalist physician specialties with expertise in the care of older, medically complex adults with polypharmacy such as Geriatrics and General Internal Medicine will complement existing care programs to meet this rising demand.

Finally, at the policy level, decision makers and health systems are increasingly focused on the delivery of high-value care at the end of life to reduce suffering and improve quality, for the lowest possible cost. This renewed attention is propelled by our ability to extend life without assurance to relieving a high burden of suffering and accompanying health expenditure.[64] Decision makers are faced with challenges related

to controlling costs while meeting needs of patients. As discussed in section 1.2.6, palliative care appears to be associated with reduced costs, although further work is required to confirm these findings. Certainly, the associated reductions in acute healthcare use, which account for 75% of the costs of end-of-life care, hold promise that palliative care can deliver high-quality care to patients for equal or lower costs than before.[11] Ongoing challenges remain about how best to make decisions about allocation of constrained resources to expand palliative care and its opportunity costs.

Decision makers must also be aware of the rising demand for palliative care and ensure that future health system planning is adequately funded to continue expansion of palliative care programs and its staffing. In addition to the programs themselves, meeting the demands of physician training and adequate reimbursement commensurate with their training and responsibilities (including care coordination and 24/7 on-call services) require focused discussion, planning and investment.

5.5 Implications for Research

The completion of this thesis raised more questions than it answered. Thankfully, this provided the opportunity to reflect and develop a research agenda for high-value palliative care to address existing knowledge gaps while laying down a road map for future work. This builds on recently a published agenda that uses a framework of *who, what, where, when* and *how?*[127] I have added a *why?* category that focusses on the potential for palliative care to deliver high-value end-of-life care and identifies the key issues requiring study to advance the field in this area of inquiry.

5.5.1 *Who* is able to access and benefit from palliative care?

Ensuring equitable access to high-quality palliative care remains one of the largest challenges facing healthcare systems. Several studies have identified several patient-, provider- and system-level factors that are associated with limited access to palliative care. Approximately 60% of people receive palliative care in their last year of life. Fewer than 1 in 4 Canadians receive home palliative care at the end of life.[44,65,137,177] Among those that die in hospital, one third do not access palliative care and 88% had no prior records of having palliative care needs, despite many of them having multiple interactions with the healthcare system in the last year of life.[44,178] Age, sex, geographic region, type of illness, ethnicity and immigrant status are all associated with limitations in access to palliative care.[44–46,65–67,179–181] Further, provider-level deficiencies in palliative care may be related to differences in specialist self-rated knowledge of end-of-life care or recognition of their patient's palliative needs subsequent referral during their course of illness.[160,161,164,170–173]

Virtual care involves the use of telemedicine and videoconferencing to deliver health services remotely.[182] Virtual care has the potential to improve health outcomes, expand the pool of palliative care providers and increase equitable access to the best possible care when and where patients need it.[182–192] During the COVID-19 pandemic, the use of virtual palliative care was rapidly upscaled across the healthcare system to address support gaps for patients while preventing transmission.[193] Notably, there was little consideration of issues related to health equity and access.[194–196] This created a unique opportunity to study virtual palliative care for patients at the end of life to inform its delivery in the post-pandemic era.[188,197–199]

Ultimately, a substantial body of work is needed to evaluate innovative means by which to overcome gaps in access to palliative care and ensure equitable access to high-quality end-of-life care for all Canadians.

5.5.2 *What* constitutes a palliative care intervention?

One of the important issues that arose during and following the completion of the systematic review and meta-analysis of palliative care in noncancer illness was how to define a palliative care intervention. Currently, there are no established standards that set out definitions of a palliative care intervention, which has led to substantial variation in research. Prior work examining different models of palliative care all identified significant heterogeneity in how palliative care is defined and delivered as limitations to more robust evaluation.[69,92–94,200,201] This heterogeneity also has direct implications for policy planning as systems struggle with how to organize and scale palliative care programs across the country to meet growing demands. It is challenging to design palliative care programs and achieve their associated benefits when there is considerable variation in the specific elements of the intervention, its timing and its "dose".

In our systematic review, we used the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care as an intentionally inclusive framework to define a palliative care intervention.[77] The NCP guidelines outline eight domains that capture the fundamental principles of palliative care that should be integrated into the care of seriously ill patients. Trials of palliative care interventions selected for full review were subsequently included if they contained elements of care that addressed ≥2 of 8 of the palliative care domains. This strategy was chosen to

maintain consistency with prior systematic reviews and to facilitate comparison.[69] However, our study did not place further restrictions on the timing of initiation or frequency of palliative care delivery.

One approach to accomplish this would be to obtain patient, caregiver, researcher and clinician perspectives using the Delphi method to establish a consensus-based definition of a palliative care intervention. The Delphi method enables efficient access to a broad range of experts with the aim of achieving consensus through a process where successive stages depend on results from the previous round.[202,203]

The establishment of a standard definition of a palliative care intervention would provide researchers with a framework to study and compare the benefits of palliative care more directly, and policy makers with a scaffold in which to build future palliative care programs.

5.5.3 *Where* and *when* should palliative care be initiated and delivered to maximize its benefits across different patient groups?

The focus of clinicians, decision makers and health services researchers is shifting from an examination of the efficacy of palliative care across distinct types of serious illness, to an examination of the successful design of palliative care programs to scale and implement them. Part of this design entails determining the optimal timing and care setting for palliative care initiation and delivery.

A population-based cohort study of 230,921 adults who died in Ontario demonstrated differences in the magnitude of association between the late initiation of

palliative care (<60 days prior to death) and healthcare use at the end of life across types of serious illness compared to early initiation (≥60 days prior to death). Here, late palliative care was associated with a 3.25-fold higher odds of acute healthcare use at the end of life in patients dying of chronic organ failure, a 3.05-fold higher odds in patients dying of dementia, and a 2.31-fold higher odds in patients dying of cancer.[47] Other work demonstrated important effects of early initiation of palliative care according to the care setting in which it was initiated and for specific types of illness such as cancer.[166,167,204–209]

As the field evolves to standardize the definition of a palliative care intervention, research is needed to clarify the optimal timing and care setting in which to initiate and deliver it across different types of illness.[66,68,69] Persistent challenges remain in how to identify patients who would benefit from a palliative approach, which may be related to their disease, prognosis and underlying palliative needs.[207]

5.5.4 *How* should palliative care be delivered to maximize its benefits and ensure equitable access to it?

The heterogeneity in timing, delivery and models of palliative care, along with patient-, provider- and system-level factors associated with limited access to palliative care create sizeable challenges in the design of effective palliative care programs. Based on the work presented in this thesis, I believe that there are three models of palliative care delivery that require priority evaluation using robust research methods. First, for virtual palliative care, it is imperative that we (1) characterize gaps in access by identifying patient, provider and health system predictors of receiving virtual palliative care, (2) characterize the potential benefits of virtual palliative care by identifying

patient, provider and health system predictors associated with reduced healthcare use and a home death among its users, and (3) understand the experience of patients, caregivers and providers using virtual palliative care and their perceptions about potential facilitators and barriers. Second, a comparison of specialist, generalist and stepped models of care delivery, such as those used in the care of mental health treatment, is essential to aid in healthcare planning to meet the growing demand for palliative care services that are outstripping current supply.[93,127,210,211] Third, evidence on the efficacy of how specialist and generalist palliative care optimally collaborate in the care of their patients with serious illness is lacking. Conceptual models of specialist and generalist palliative care delivery can be dichotomized into two distinct types. In a "handoff" model, providers such as oncologists effectively hands over the entirety of care of their patient to the palliative care team until death. Conversely, a "handshake" model utilizes the principles of co-management whereby providers maintain a longitudinal relationship with their patient alongside the palliative care team until death.[212] Using a stepped care approach, specialist palliative care teams are available for consultation related to complex or refractory cases. Handshake models may also benefit providers as they are able to further gain skills in the care of seriously ill patients from their palliative care colleagues. Preliminary work described how palliative care was being delivered at a population level, including different models of generalist and specialist care, but a broader understanding of its impact is still limited.[45,137]

5.5.5 *Why* should health systems continue to expand investment in palliative care?

Equally important to defining a palliative care intervention may be to justify the importance of palliative care to patients, providers and healthcare systems more broadly. The primary goal of palliative care is to improve quality of life and reduce symptom burden. Although not its intended purpose, one of the potentially beneficial consequences of palliative care may be to simultaneously maximize high-value care by reducing healthcare use and its associated costs.[69,127] The thesis work presented here supports the role of palliative care in providing high-value end-of-life care to people dying with cancer and most noncancer illness. We found that palliative care reduces symptoms, healthcare use and potentially burdensome interventions near the end of life.[45,66,68] We also found that palliative care increases the odds of dying at home – a place that most people prefer and a recognized indicator of high-quality end-of-life care.[51–53]

We recently completed a narrative review of 60 studies involving 87,609 patients, caregivers, healthcare providers, decision makers and members of the general public found conflicting results on the importance of life extension at the end of life (unpublished data). Patients and caregivers consistently prioritized comfort at the end of life. Yet there was substantial heterogeneity in viewpoints within groups of study participants as well as consistent discordance between society's and patients' views. Most studies found that all groups prioritized improvements in health-related quality of life (HRQOL) over life extension at the end of life. Taken together, these results suggest that most people prioritize interventions that improve HRQOL at the end of life, and that they value these gains more so than interventions that extend life. However, individual preferences vary widely. Our findings also suggest that patients value care that

improves the *process* of dying by allowing them to remain comfortable, to spend time with family and to avoid a prolonged death. Therefore, a 'one-size-fits-all' approach to care and aggregate measures of its success are unlikely to align with any individual patient or caregiver preferences at the end of life.[213]

In light of these findings and framed within the Theory of Value, the promise of palliative care to improve value in healthcare couldn't be stronger.[78] Palliative care focusses on meeting patients in the moment and preparing them to make decisions optimally aligned with their underlying preferences and goals of care. It also focuses on relieving suffering throughout the process of dying. Further, the majority of patients prefer comfort with less costly acute care use near the end of life. It is therefore unlikely that the costs related to the delivery of high-quality palliative care will be greater than the current costs of care delivery at end of life. Indeed, current evidence suggests that measured costs are lower among patients receiving palliative care in multiple health care settings, although formal economic evaluations on cost-effectiveness that include direct out-of-pocket costs to the patient and caregiver are still needed. As society and healthcare systems gain a greater understanding of value at the end of life in the context of the "patient good", new models of palliative and end-of-life care can develop to achieve this good. The current challenges facing healthcare systems lie in defining and measuring value at end of life and the ability of new care models to achieve high-value care.

Table 5.1 – A proposed research agenda for palliative care and proposed solutions.

Research Challenge	Proposed Solution

Who is able to access and benefit from palliative care?	1. Creation of a prospective national palliative care registry of all patients with serious illness, limited life expectancy and measured palliative care needs. Using existing administrative data infrastructure, the registry would track the delivery of care across all settings, changes in living arrangements (such as loss of a caregiver or institutionalization), changes in palliative needs, trajectory of functional decline and important patient- and policy-facing outcomes. 2. Understand patient, provider and health system factors that influence receipt of palliative care within and across different types of illnesses and at different timing and disease and functioning inflection points for patients. 3. Identify patients most likely to benefit (disease, prognosis and needs).
What constitutes a palliative care intervention?	1. Define what constitutes palliative care and its key elements through the completion of a modified Delphi study of patients, caregivers, clinicians and researchers to define and standardize its delivery. 2. Validate the capture of physician-delivered palliative care in administrative data using existing physician fee codes through the completion of a validation study measuring the sensitivity, specificity, positive and negative predictive values of receipt of palliative care by all providers.
Where is palliative care optimally initiated and delivered to maximize its benefits across different patient groups?	1. Identify optimal care settings for the initiation of palliative care and its ongoing delivery.
When should palliative care be initiated for patients according to their	1. Identify the optimal timing of the initiation of palliative care by leveraging the creation of a prospective national

disease, prognosis and palliative care needs?	palliative care registry to prevent future suffering, which may differ between different populations of patients with different diseases, prognoses and needs.
How should palliative care be delivered to maximize its benefits and ensure equitable access to it?	1. Evaluate innovative models of palliative care to ensure equitable access to effective high-quality end-of-life care. Examples include evaluation of: 1) Virtual palliative care 2) Generalist versus specialist palliative care 3) "Handshake" versus "handoff"
Why should health systems continue to expand investment in palliative care?	1. It is essential to define what constitutes high-value end-of-life care and to develop effective and reliable methods to measure it throughout a patient's illness to evaluate the ability of palliative care to deliver high-value end-of-life care.

5.6 Summary

The primary goal of this thesis was to build the evidence base for palliative care in patients with noncancer illness to inform clinical practice and policy development in the design of new palliative care programs to improve end-of-life care. This goal, as well as the three specific project objectives, have been met. The methodology used to complete this substantial body of work leveraged diverse analytic methods to minimize bias, demonstrating a broad range of approaches to conduct policy-shaping healthcare research. These thesis findings highlight the potential benefits of palliative care in select noncancer illness and identified significant knowledge gaps related to the role of palliative care in people with other common noncancer illnesses. They will help inform ongoing efforts to scale existing palliative care programs to increase access through sustained investment in physician training and optimization of current models of

collaborative palliative care. These are essential steps in the development and refinement of care models to inform the equitable expansion of palliative care and deliver the best possible end-of-life care when and where patients need it.

6 References

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