JAMA | Original Investigation

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

A Systematic Review and Meta-analysis

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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 health care use, quality of life (QOL), and symptom burden in adults with chronic noncancer illnesses.

DATA SOURCES MEDLINE, Embase, CINAHL, PsycINFO, 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 at least 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 OUTCOMES AND MEASURES Acute health care 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-Palliative Care scale (range, 0 [worst] to 184 [best]; minimal clinically important difference, 9 points) and symptoms translated to units of the Edmonton Symptom Assessment Scale global distress score (range, 0 [best] to 90 [worst]; minimal clinically important difference, 5.7 points).

RESULTS Twenty-eight trials provided data on 13 664 patients (mean age, 74 years; 46% were women). Ten trials were of heart failure (n = 4068 patients), 11 of mixed disease (n = 8119), 4 of dementia (n = 1036), and 3 of chronic obstructive pulmonary disease (n = 441). Palliative care, compared with usual care, was statistically significantly associated with less emergency department use (9 trials [n = 2712]; 20% vs 24%; odds ratio, 0.82 [95% CI, 0.68-1.00]; I^2 = 3%), less hospitalization (14 trials [n = 3706]; 38% vs 42%; odds ratio, 0.80 [95% CI, 0.65-0.99]; I^2 = 41%), and modestly lower symptom burden (11 trials [n = 2598]; pooled standardized mean difference (SMD), −0.12; [95% CI, −0.20 to −0.03]; I^2 = 0%; Edmonton Symptom Assessment Scale score mean difference, −1.6 [95% CI, −2.6 to −0.4]). Palliative care was not significantly associated with disease-generic QOL (6 trials [n = 1334]; SMD, 0.18 [95% CI, −0.24 to 0.61]; I^2 = 87%; Functional Assessment of Chronic Illness Therapy-Palliative Care score mean difference, 4.7 [95% CI, −6.3 to 15.9]) or disease-specific measures of QOL (11 trials [n = 2204]; SMD, 0.07 [95% CI, −0.09 to 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 statistically significantly associated with less acute health care 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.

JAMA. 2020;324(14):1439-1450. doi:10.1001/jama.2020.14205

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Chronic noncancer illness, such as heart failure (HF), chronic obstructive pulmonary disease (COPD), and dementia, are common and associated with high health care use, symptom burden, and disability and reduced quality of life (QOL).[1-6] Palliative care focuses on improving QOL, reducing suffering, and helping with decision-making for patients with serious illness and their caregivers.[7] 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 with cancer.[8] Application of current evidence for palliative care to those with noncancer illness may therefore restrict its applicability because these chronic diseases have a very different illness trajectory.[9-12]

Three systematic reviews of randomized clinical trials (RCTs) of palliative care interventions reported associations with higher patient and caregiver QOL and lower symptom burden.[7,13,14] 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.

The current study measured the association between palliative care and health care 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 and 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 health care use, QOL, and symptom burden in adults with noncancer illness.

Key Points

Question Is receipt of palliative care interventions associated with lower acute health care use and better patient-centered 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 statistically significantly associated with less acute health care 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 health care use and modestly lower symptom burden, although analyses for some outcomes were based predominantly on studies of patients with heart failure, which may limit the generalizability of these findings to other chronic illnesses.

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 Statement 27-item checklist.[15]

Identification and Selection of Studies

MEDLINE, Embase, CINAHL, PsychINFO, and PubMed were searched for articles published from inception to April 18, 2020. The primary author (K.L.Q.) and a health sciences librarian (D.H.) conducted the searches (eAppendix 1 in the Supplement). 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 1 in the Supplement). RCTs with a palliative care intervention were included for full review if they were conducted in adults (aged ≥18 years) with a primary diagnosis of HF, COPD, kidney failure, dementia, cirrhosis, or stroke. These diseases represent the most common terminal noncancer conditions and are the most well-studied in palliative care.[7,13,14] Trials that enrolled multiple groups of patients, each with different primary diseases, were categorized as "mixed disease." Because many patients included in palliative care trials may also have cancer, studies that included at least 50% of patients with comorbid terminal cancer were excluded. Trials of palliative care interventions selected for full review were subsequently included (regardless of whether they included specialized palliative care clinicians) if they contained elements of care that addressed at least 2 of 8 domains outlined in the 2018 National Consensus Project on Clinical Practice Guidelines for Quality Palliative Care.[16] 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: 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 at least 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.[7] Studies that reported on at least 1 of the following 3 outcomes of interest were included: health care use (hospitalizations or emergency department [ED] 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.[17] The tool uses a series of questions within a set of domains of bias that

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assess a trial's design, conduct, and reporting. Within each domain, the risk of bias was independently assessed by 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 by having "some concerns" about the risk of bias for an individual trial (eAppendix 2 in the Supplement). This study included both objective (eg, hospitalizations, ED use) and subjective (eg, patient-reported QOL and symptom measures) outcomes. Each type of outcome was assessed separately with respect to its risk of bias 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 health care use (ED use and hospitalization), QOL, and symptom burden. To be included in the meta-analysis, data from each trial were required to be reported as the percentage of patients with an ED visit or hospitalization during follow-up or as the mean and SD of QOL or symptom scores at baseline and end-of-study follow-up (range, 1-13 months). Health care use was analyzed as the percentage of patients with at least 1 ED visit or hospitalization during follow-up, because access to patient-level data to account for individual follow-up time were 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 (SMDs) corrected for scale directionality, calculated using a Hedges-adjusted g estimator to correct for small sample bias (eAppendix 3 in the Supplement).[18] 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.[19] 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 SD for the specific scale from an RCT of a palliative intervention in patients with advanced HF (eAppendix 3 in the Supplement). The SMDs from the QOL outcomes were translated to the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal) scale (range, 0 [worst] to 184 [best]; minimal clinically important difference, 9 points), a validated patient-reported measure of QOL in people with serious illness.[20] For measures of symptom burden, the SMDs were translated to the Edmonton Symptom Assessment Scale (ESAS) score (range, 0 [best] to 90 [worst]; minimal clinically important difference, 5.7 points), a validated patient-reported measure that is commonly used in palliative care populations.[21]

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, including 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.[22] 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.[10] 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 greater than 50% is considered to represent significant heterogeneity, which was taken into account when interpreting the findings.[23] In meta-analyses, 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 of funnel plots (eFigure 5 in the Supplement).

A set of secondary analyses was 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 less than or equal to 3 months compared with greater than 3 months,[7] 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,[24] 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 or less and greater than 3 months (range, 1-13 months), because these periods were considered clinically relevant.[7] Outcome measures were recorded using the longest available follow-up time for studies that reported outcomes for both 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 (ie, who were enrolled in trials of mixed disease), because these are recognized as having unique trajectories of functional decline and may influence a person's health care needs and subsequent use[9-12]; (2) used a palliative care intervention involving an interdisciplinary care team; and (3) used a palliative care intervention involving home-based palliative care, because there is evidence to support its efficacy using both of these approaches.[25-28] 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.[18] Predefined sensitivity analyses limited to trials at low risk of bias were performed on all

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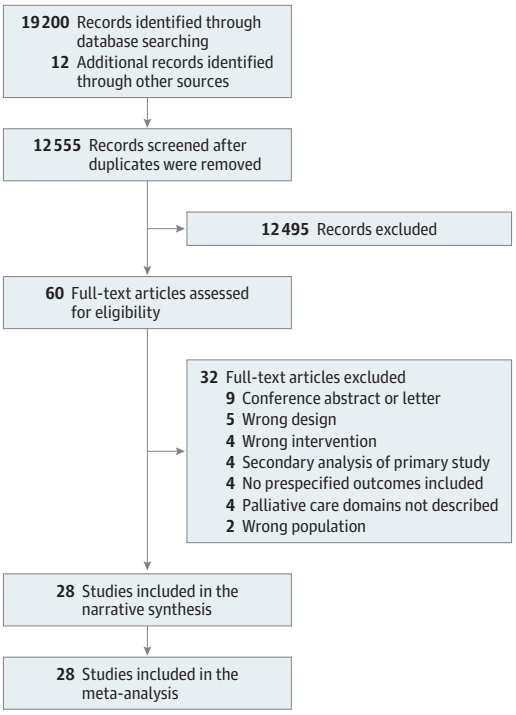
Figure 1. Literature Search to Identify Randomized Clinical Trials of Palliative Care Interventions



outcomes for which a sufficient number of trials made it possible.

Statistical significance was determined using a 2-sided error threshold of .05. Because of the potential for type I 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.

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 years; 46% were women) were included in the final analysis (**Figure 1**). Ten trials (36%) were of patients with a primary diagnosis of HF (n = 4068),[29-37] 11 (39%) were of patients with mixed disease (ie, enrolled multiple groups of patients with different primary diseases; n = 8119),[38-48] 4 (14%) were of patients with a primary diagnosis of dementia (n = 1036),[49-52] and 3 (11%) were of patients with a primary diagnosis of COPD (n = 441).[53-55] 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 comorbid diagnoses was 65% (19 trials) for HF, 42% (14 trials) for COPD, 14% (9 trials) for stroke, 42% (8 trials) for diabetes, 23% (5 trials) for chronic kidney disease, and 16% (7 trials) for cancer. Across all studies, 24.3% of patients (SD, 26.4%) died. Fourteen trials (50%) were conducted in the outpatient setting, 10 (36%) in the inpatient setting, and 4 (14%) involved both inpatient and outpatient care. Eighteen studies (64%) were conducted in the United States; 3 in the United Kingdom (11%); 2 in Canada (7%); 1 each in 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 26 trials assessed objective outcomes. The risk of bias for each trial is reported in eTables 5 and 6 in the Supplement.

There was a median (range) of 5 (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 address 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). All trials used usual care as the comparator group. Some elements of usual care included a prehospital discharge referral to palliative care[34]; telemonitoring[33]; ad hoc visits in a clinic or from a home-visiting general practitioner or palliative care physician[31,32,34]; or education on diet, exercise, advanced care planning, and palliative care[37,41] (eTables 2, 3, and 4 in the Supplement).

Acute Health Care Use

ED use was assessed in 10 trials; 8 were at high risk of bias and 2 were at some concerns of risk of bias. Six trials involved patients with mixed disease, 2 involved patients with HF, and 2 involved patients with dementia.[29,38,40,43-45,48,50,52,56] Nine studies (n = 2712 patients) could be pooled in the meta-analysis because 1 study reported data in a format that was not possible to include.[29,38,40,43,44,48,50,52,56] In the primary analysis, palliative care, compared with usual care, was significantly associated with a lower percentage of patients with ED use (20% [95% CI, 12%-28%] vs 24% [95% CI, 13%-34%]; odds ratio [OR], 0.82 [95% CI, 0.68-1.00]; I^2 = 3%) (**Figure 2**). In the secondary meta-regression analysis, the presence of a palliative care physician statistically significantly explained some of the observed differences in ED use, whereas there was no significant association with HF, mixed disease, dementia, or follow-up time (eTable 7 in the Supplement). In analyses limited to trials of palliative care interventions that involved 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 less ED use was not significant (eFigure 1 and eTable 7 in the Supplement). An analysis of ED use restricted to trials at low risk of bias could not be performed because none existed.

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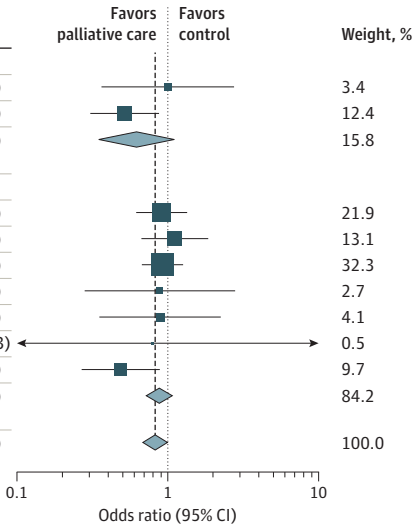
Figure 2. Random-Effects Meta-analysis of the Association Between Palliative Care and Health Care Use Among Patients With Noncancer Illness

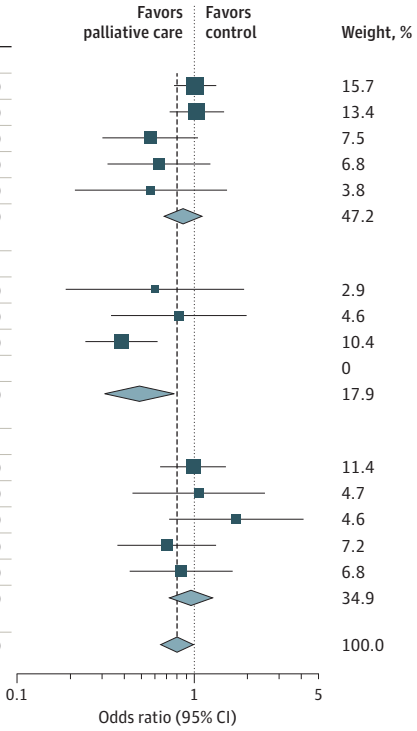
A Emergency department use

Study	Palliative care: No. of events/ No. of total patients	Palliative care: Crude rate	Control: No. of events/ No. of total patients	Control: Crude rate	Disease	Odds ratio (95% CI)	Weight, %
Some concerns of bias							
Radwany et al,[40] 2014	10/40	0.25	10/40	0.25	Mixed	1.00 (0.36-2.75)	3.4
Brumley et al,[43] 2007	31/152	0.20	48/145	0.33	Mixed	0.52 (0.31-0.87)	12.4
Random-effects model Heterogeneity: $I^2 = 22\%$; $\tau^2 = 0.0475$; $P = .26$						0.62 (0.35-1.10)	15.8
High risk of bias							
Van Spall et al,[29] 2019	56/248	0.23	81/334	0.24	Heart failure	0.91 (0.62-1.34)	21.9
Van den Block et al,[38] 2019	33/206	0.16	37/253	0.15	Mixed	1.11 (0.67-1.85)	13.1
Possin et al,[52] 2019	199/452	0.44	110/239	0.46	Dementia	0.92 (0.67-1.26)	32.3
Agar et al,[50] 2017	6/64	0.09	7/67	0.10	Dementia	0.89 (0.28-2.80)	2.7
Aiken,et al,[48] 2006	10/100	0.10	10/90	0.11	Mixed	0.89 (0.35-2.25)	4.1
Rabow et al,[44] 2004	1/50	0.02	1/40	0.02	Mixed	0.80 (0.05-13.13)	0.5
Harrison et al,[46] 2002	27/92	0.29	46/100	0.46	Heart failure	0.49 (0.27-0.89)	9.7
Random-effects model Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = .58$						0.88 (0.72-1.07)	84.2
Random-effects model Heterogeneity: $I^2 = 3\%$; $\tau^2 = 0.0027$; $P = .41$ Residual heterogeneity: $I^2 = 0\%$; $P = .54$						0.88 (0.68-1.00)	100.0



B Hospitalization

Study	Palliative care: No. of events/ No. of total patients	Palliative care: Crude rate	Control: No. of events/ No. of total patients	Control: Crude rate	Disease	Odds ratio (95% CI)	Weight, %
Low risk of bias							
Van Spall et al,[29] 2019	145/400	0.36	180/500	0.36	Heart failure	1.01 (0.77-1.33)	15.7
Possin et al,[52] 2019	124/452	0.27	64/239	0.27	Dementia	1.03 (0.73-1.47)	13.4
Bekelman et al,[32] 2018	19/158	0.12	31/159	0.19	Heart failure	0.56 (0.30-1.05)	7.5
Rogers et al,[31] 2017	43/75	0.57	51/75	0.68	Heart failure	0.63 (0.32-1.23)	6.8
Wong et al,[34] 2016	9/43	0.21	13/41	0.32	Heart failure	0.57 (0.21-1.53)	3.8
Random-effects model Heterogeneity: $I^2 = 25\%$; $\tau^2 = 0.0198$; $P = .25$						0.86 (0.68-1.10)	47.2
Some concerns of bias							
Brännström et al,[35] 2014	6/36	0.17	9/36	0.25	Heart failure	0.60 (0.19-1.91)	2.9
Radwany et al,[40] 2014	20/40	0.50	22/40	0.55	Mixed	0.82 (0.34-1.97)	4.6
Brumley et al,[43] 2007	55/152	0.36	86/145	0.59	Mixed	0.39 (0.24-0.62)	10.4
Ahronheim et al,[51] 2000	48/48	1.00	51/51	1.00	Dementia		0
Random-effects model Heterogeneity: $I^2 = 14\%$; $\tau^2 = 0.0273$; $P = .31$						0.49 (0.31-0.77)	17.9
High risk of bias							
Van den Block et al,[38] 2019	51/197	0.26	65/248	0.26	Heart failure	0.98 (0.64-1.51)	11.4
Agar et al,[50] 2017	13/64	0.20	13/67	0.19	Dementia	1.06 (0.45-2.50)	4.7
Rabow et al,[44] 2004	35/50	0.70	23/40	0.57	Mixed	1.72 (0.72-4.12)	4.6
Harrison et al,[56] 2002	22/92	0.24	31/100	0.31	Heart failure	0.70 (0.37-1.33)	7.2
Zimmer et al,[45] 1985	25/82	0.30	26/76	0.34	Mixed	0.84 (0.43-1.64)	6.8
Random-effects model Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = .58$						0.96 (0.72-1.27)	34.9
Random-effects model Heterogeneity: $I^2 = 41\%$; $\tau^2 = 0.0550$; $P = .06$ Residual heterogeneity: $I^2 = 5\%$; $P = .39$						0.80 (0.65-0.99)	100.0



Data are presented as the odds ratios and 95% CIs (error bars) of at least 1 emergency department visit 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 ratios and 95% CIs. The dashed line indicates the pooled effect estimate and the dotted line depicts a null effect.

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 of risk of bias. Four trials involved patients with mixed disease, 8 involved patients with HF, 3 involved patients with dementia, and 1 involved patients with COPD.[31,32,34-36,40,44,45,50,51,56] Fourteen studies (n = 3706 patients) could be pooled in the

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meta-analysis because 1 study reported data in a format that was not possible to include.[29,31,32,34,35,38,40,43-45,50-52,56] In the primary analysis, palliative care, compared with usual care, was significantly associated with less hospitalized patients (38% [95% CI, 25%-50%] vs 42% [95% CI, 30%-54%]; OR, 0.80 [95% CI, 0.65-0.99]; I^2 = 41%) (Figure 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 HF, mixed disease, dementia, or follow-up time (eTable 7 in the Supplement). In analyses limited to trials of palliative care interventions that involved 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 a lower percentage of hospitalization among patients was not significant (eFigure 1 and eTable 7 in the Supplement). 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).

Disease-Generic and Disease-Specific QOL

QOL 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 involved patients with mixed disease.[29,31,34,35,37,39,40,57] Six studies (n = 1334) 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.[29,34,35,37,39,57] 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 to 0.61]; I^2 = 87%; FACIT-Pal score mean difference, 4.7 [95% CI, −6.3 to 15.9]) (**Figure 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 HF, mixed disease, or follow-up time (eTable 7 in the Supplement). In analyses limited to trials of palliative care interventions that involved an interdisciplinary care team (pooled SMD, 0.18 [95% CI, −0.29 to 0.64]) and home visits (pooled SMD, 0.15 [95% CI, −0.40 to 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 to 0.61]) and cancer (pooled SMD, 0.19 [95% CI, −0.31 to 0.69]), the association with higher disease-generic QOL was not significant (eFigure 2 and eTable 7 in the Supplement). When the analyses 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 score mean difference, 9.7 [95% CI, 0.5-18.5]) (Figure 3).

QOL was assessed using disease-specific measures in 12 trials; 6 were at high risk of bias and 6 were at low risk of bias. Eight trials involved patients with HF, 2 involved patients with mixed disease, 1 involved patients with dementia, and 1 involved patients with COPD.[31-37,39,42,52,54,56] Eleven studies (n = 2204) could be pooled in the disease-specific QOL meta-analysis because 1 study reported data in a format that was not possible to include.[31-37,39,42,52,56] In the primary analysis, palliative care was not significantly associated with disease-specific measures of QOL (pooled SMD, 0.07 [95% CI, −0.09 to 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, HF, mixed disease, or follow-up time (eTable 7 in the Supplement). In the other secondary analyses, interventions that involved 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%) were 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 and eTable7 in the Supplement). When the analyses 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 to 0.43]; I^2 = 68%) (Figure 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 of risk of bias. Six trials involved patients with HF, 6 involved patients with mixed disease, and 2 involved patients with dementia.[31-34,36-39,41,42,44,49,50,53] Eleven studies (n = 2598) could be pooled in the meta-analysis because 3 studies reported data in a format that was not possible to include.[32-34,37-39,41,42,44,49,53] In the primary analysis, palliative care was significantly associated with lower symptom burden (pooled SMD, −0.12 [95% CI, −0.20 to −0.03]; I^2 = 0%; ESAS mean difference, −1.6 [95% CI, −2.6 to −0.4]), which would translate to an average of a 0.2-point decrease across all subdomains on the ESAS (**Figure 4**). In the secondary meta-regression analyses, the presence of a palliative care physician, HF, and mixed disease explained some of the observed difference in symptoms, whereas there was no significant association with follow-up time (eTable 7 in the Supplement). In the other secondary analyses, interventions that involved an interdisciplinary care team were significantly associated with lower symptom burden (pooled SMD, −0.11 [95% CI, −0.19 to −0.02]; I^2 = 0%; ESAS mean difference, −1.5 [95% CI, −2.5 to −0.3]). In analyses limited to trials of palliative care interventions that involved home visits, the association with lower symptom burden was not significant (pooled SMD, −0.15 [95% CI, −0.34 to 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 to −0.03]; I^2 = 0%; ESAS mean difference, −1.6 [95% CI, −2.6 to −0.4]) and cancer (pooled SMD, −0.16 [95% CI, −0.31 to −0.01]; ESAS mean difference, −2.1 [95% CI, −4.1 to −0.1]), the association with lower symptom burden was significant (eFigure 3 and eTable 7 in the Supplement). When the analyses of symptoms were restricted to trials at low risk of bias, no significant association was observed (pooled SMD, −0.15 [95% CI, −0.30 to 0.01]) (Figure 4).

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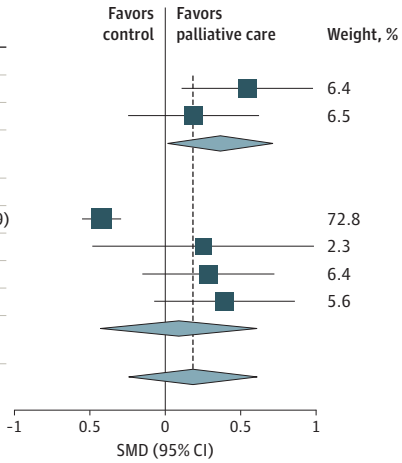
Figure 3. Random-Effects Meta-analysis of the Association Between Palliative Care and Quality of Life (QOL) Among Patients With Noncancer Illness

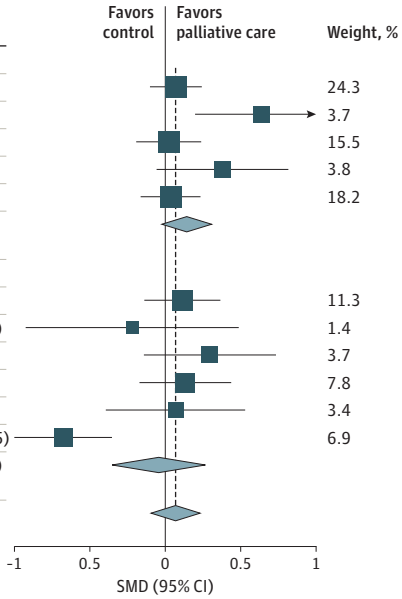
A Disease-generic measure of quality of life

Study	Palliative care: Total No. of patients	Palliative care: SMD	Control: Total No. of patients	Control: SMD	Scale	Disease	SMD (95% CI)	Weight, %
Low risk of bias								
Wong et al,[34] 2016	43	0.76	41	0.05	McGill QOL	Heart failure	0.54 (0.11 to 0.98)	6.4
Higginson et al,[39] 2014	42	0.22	40	0.03	EQ-5D	Mixed	0.19 (-0.25 to 0.62)	6.5
Random-effects model Heterogeneity: I^2 = 22%; τ^2 = 0.0142; P = .26							0.37 (0.02 to 0.71)	
High risk of bias								
Van Spall et al,[29] 2019	606	-0.04	380	0.36	EQ-5D	Heart failure	-0.42 (-0.55 to -0.29)	72.8
O'Donnell et al,[37] 2018	16	0.34	13	0.04	FACIT-Sp	Heart failure	0.25 (-0.48 to 0.99)	2.3
Rogers et al,[31] 2017	41	0.57	40	0.28	FACIT-PAL	Heart failure	0.29 (-0.15 to 0.72)	6.4
Brännström et al,[35] 2014	36	0.63	36	0.18	EQ-5D	Heart failure	0.39 (-0.07 to 0.86)	5.6
Random-effects model Heterogeneity: I^2 = 86%; τ^2 = 0.2256; P <.01							0.09 (-0.43 to 0.61)	
Random-effects model Heterogeneity: I^2 = 87%; τ^2 = 0.2306; P <.001 Residual heterogeneity: I^2 = 82%; P <.001							0.18 (-0.24 to 0.61)	



B Disease-specific measure of quality of life

Study	Palliative care: Total No. of patients	Palliative care: SMD	Control: Total No. of patients	Control: SMD	Scale	Disease	SMD (95% CI)	Weight, %
Low risk of bias								
Possin et al,[52] 2019	368	-0.19	201	-0.27	QoL-AD	Dementia	0.07 (-0.10 to 0.24)	24.3
Wong et al,[34] 2016	43	0.78	41	0.05	CHQ-C	Heart failure	0.64 (0.20 to 1.07)	3.7
Bekelman et al,[33] 2015	164	0.77	167	0.78	KCCQ CRQ	Heart failure	0.02 (-0.19 to 0.24)	15.5
Higginson et al,[39] 2014	42	0.62	40	0.22	HRQOL	Mixed	0.38 (-0.06 to 0.82)	3.8
Gade et al,[39] 2008	199	0.78	191	0.80	Self-reported QOL	Mixed	0.04 (-0.16 to 0.23)	18.2
Random-effects model Heterogeneity: I^2 = 52%; τ^2 = 0.0171; P = .08							0.14 (-0.02 to 0.31)	
High risk of bias								
Bekelman et al,[32] 2018	121	0.29	121	0.15	KCCQ	Heart failure	0.11 (-0.14 to 0.37)	11.3
O'Donnell et al,[37] 2018	16	0.46	15	0.62	KCCQ	Heart failure	-0.22 (-0.93 to 0.49)	1.4
Rogers et al,[31] 2017	41	1.34	40	0.94	KCCQ	Heart failure	0.30 (-0.14 to 0.73)	3.7
Sidebottom et al,[36] 2015	79	0.61	88	0.55	MLHFQ	Heart failure	0.13 (-0.17 to 0.44)	7.8
Brännström et al,[35] 2014	36	2.82	36	1.50	KCCQ	Heart failure	0.07 (-0.39 to 0.53)	3.4
Harrison et al,[56] 2002	79	-1.00	76	-0.33	MLHFQ	Heart failure	-0.68 (-1.00 to -0.35)	6.9
Random-effects model Heterogeneity: I^2 = 75%; τ^2 = 0.1062; P <.01							-0.04 (-0.35 to 0.27)	
Random-effects model Heterogeneity: I^2 = 68%; τ^2 = 0.0457; P <.001 Residual heterogeneity: I^2 = 69%; P <.001							0.07 (-0.09 to 0.23)	



Data are presented as the means and 95% CIs (error bars) of the change in QOL 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 differences (SMDs) and 95% CIs. The dashed line indicates the pooled effect estimate and the black vertical line depicts a null effect. CHQ-C indicates Chronic Heart Failure Questionnaire Chinese; CRQ Chronic Respiratory Questionnaire; EQ-5D, EuroQol-5D; FACIT-PAL, Functional Assessment of Chronic Illness Therapy-Palliative Care; FACIT-Sp, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; HRQOL, Health-Related Quality of Life; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; and QoL-AD, Quality of Life in Alzheimer's Disease .

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 of risk of bias. Three trials involved patients with HF, 3 involved patients with mixed disease, 2 involved patients with COPD, and 1 involved patients with dementia.[30,36,37,42,46,48,51,54,55] Seven studies (n = 5935) could be pooled in the meta-analysis because 2 studies reported data in a format that was not possible to include.[30,37,42,46,51,54,55] In a post hoc analysis, compared with usual care, palliative care was significantly associated with advance care planning, although there was considerable heterogeneity (38% [95% CI, 25%-50%] vs 42% [95% CI, 30%-54%] of patients received advance care planning; OR, 2.95 [95% CI, 1.52-5.73]; I^2 = 84%) (**Figure 5**). In the secondary meta-regression analysis, the presence of a palliative care physician, HF, COPD, and dementia

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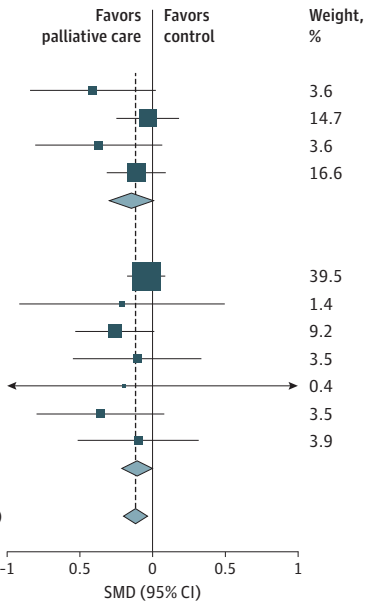
Figure 4. Random-Effects Meta-analysis of the Association Between Palliative Care and Symptoms Among Patients With Noncancer Illness

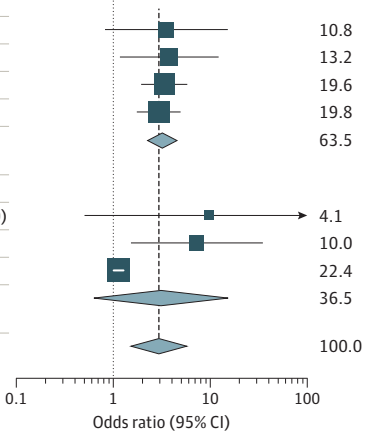
Study	Palliative care: Total No. of patients	Palliative care: SMD	Control: Total No. of patients	Control: SMD	Scale	Disease	SMD (95% CI)	Weight, %
Low risk of bias								
Wong et al,[34] 2016	43	-0.69	41	-0.15	ESAS	Heart failure	-0.41 (-0.84 to 0.02)	3.6
Bekelman et al,[33] 2015	164	-0.22	167	-0.18	PHQ-9	Heart failure	-0.03 (-0.25 to 0.18)	14.7
Higginson et al,[39] 2014	42	0	40	0.37	HADS	Mixed	-0.37 (-0.81 to 0.07)	3.6
Gade et al,[42] 2008	186	-0.68	188	-0.56	MCOHPQ Physical	Mixed	-0.11 (-0.32 to 0.09)	16.6
Random-effects model Heterogeneity: $I^2 = 16\%$; $\tau^2 = 0.0040$; $P = .31$							-0.15 (-0.30 to 0.01)	
High risk of bias								
Van den Block et al,[38] 2019	387	0.02	526	0.06	CAD-EOLD	Mixed	-0.04 (-0.18 to 0.09)	39.5
O'Donnell et al,[37] 2018	16	-0.44	15	-0.12	PHQ-8	Heart failure	-0.21 (-0.92 to 0.50)	1.4
Bekelman et al,[32] 2018	105	-0.40	105	-0.12	PHQ-9	Heart failure	-0.26 (-0.53 to 0.01)	9.2
Farquhar et al,[53] 2016	41	-0.14	38	-0.03	HADS	Mixed	-0.11 (-0.55 to 0.34)	3.5
Sampson et al,[49] 2011	7	-0.46	4	-0.11	Distress VAS	Dementia	-0.20 (-1.43 to 1.03)	0.4
Pantilat et al,[41] 2010	41	-0.53	40	-0.12	Dyspnea	Mixed	-0.36 (-0.80 to 0.08)	3.5
Rabow et al,[44] 2004	50	-0.45	40	-0.35	U California	Mixed	-0.10 (-0.52 to 0.32)	3.9
Random-effects model Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = .75$							-0.11 (-0.21 to 0.00)	
Random-effects model Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = .71$ Residual heterogeneity: $I^2 = 0\%$; $P = .63$							-0.12 (-0.20 to -0.03)	



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 dashed line indicates the pooled effect estimate and the black vertical line depicts a null effect. CAD-EOLD, End-of-Life in Dementia comfort around dying scale; ESAS indicates Edmonton Symptom Assessment Scale; HADS, Hospital Anxiety and Depression Scale; MCOHPQ, Modified City of Hope Patient Questionnaire; PHQ, Patient Health Questionnaire; SMD, standardized mean difference; and VAS, visual analog scale.

Figure 5. Random-Effects Meta-analysis of the Association Between Palliative Care and Advance Care Planning Among Patients With Noncancer Illness

Study	Palliative care: No. of events/ total No. of patients	Palliative care: Crude rate	Control: No. of events/ total No. of patients	Control: Crude rate	Disease	Odds ratio (95% CI)	Weight, %
Low risk of bias							
Janssens et al,[54] 2019	9/26	0.35	3/23	0.13	COPD	3.53 (0.82-15.17)	10.8
O'Donnell et al,[37] 2018	17/26	0.65	8/24	0.33	Heart failure	3.78 (1.17-12.19)	13.2
Au et al,[55] 2012	59/194	0.30	21/182	0.12	COPD	3.35 (1.94-5.80)	19.6
Gade et al,[42] 2008	251/275	0.91	185/237	0.78	Mixed	2.94 (1.75-4.94)	19.8
Random-effects model Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = .97$						3.20 (2.26-4.54)	63.5
Some concerns of bias							
Hopp et al,[30] 2016	4/43	0.09	0/42	0	Heart failure	9.68 (0.50-185.70)	4.1
Ahronheim et al,[51] 2000	11/48	0.23	2/51	0.04	Dementia	7.28 (1.52-34.87)	10.0
SUPPORT,[46] 1995	1061/2652	0.40	797/2152	0.37	Mixed	1.13 (1.01-1.27)	22.4
Random-effects model Heterogeneity: $I^2 = 73\%$; $\tau^2 = 1.3560$; $P = .02$						3.11 (0.63-15.28)	36.5
Random-effects model Heterogeneity: $I^2 = 84\%$; $\tau^2 = 0.5051$; $P < .01$ Residual heterogeneity: $I^2 = 35\%$; $P = .18$						2.95 (1.52-5.73)	100.0



Data are presented as the odds ratios 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 ratios and 95% CIs. The dashed line indicates the pooled effect estimate and the dotted line depicts a null effect. COPD indicates chronic obstructive pulmonary disease.

explained some of the observed differences in advanced care planning, whereas there was no significant association with mixed disease (eTable 7 in the Supplement). In the other secondary analyses, interventions involving an interdisciplinary care team were significantly associated with advance care planning (OR, 3.34 [95% CI, 2.10-5.29]; I^2 = 0%). There were

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no studies of interventions involving home visits. In analyses among the subset of trials that excluded studies that included 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 statistically significant (eFigure 4 and eTable 7 in the Supplement). 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 5).

Discussion

In this systematic review and meta-analysis of 28 randomized clinical trials of 13 664 patients with primarily noncancer illness, palliative care was associated with less health care use and modestly lower symptom burden. Although palliative care was associated with advance care planning and was not associated with better QOL, 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 patients with noncancer illness, which will inform the ongoing design and delivery of palliative care for patients, clinicians, and policy makers in health care systems.

Results of secondary analyses of factors associated with palliative care 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,[58] a responsibility that other clinicians, such as nurse practitioners, with prescribing abilities can also perform. Because 11 of 28 trials and 38% of patients in those trials had a diagnosis of HF, the results may be weighted by the benefits to patients with HF. However, because HF 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, because they were based predominantly on studies of patients with HF, 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, kidney failure, stroke, and cirrhosis, because there were few RCTs of patients with these diseases. Palliative care that provided home-based care was not associated with less health care use, lower symptom burden, or higher measures of QOL. This is surprising because hospitalization near the end of life is associated with poor QOL,[5,6,59] and 40% of people with serious illness report that they value the health services available to care for them in their home.[60] One possible explanation for these findings is that most patients enrolled in trials of palliative care interventions in this study did not die. The strongest benefits for home-based palliative care appears to be for patients who are nearing the end of their life.[27] However, the magnitude of the summary point estimates were similar to the primary analyses, but the CIs were wider, which may suggest that these secondary analyses were underpowered to detect a statistically 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.[24,61] The findings from this study support ongoing efforts by health care 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.

Previous work in this area reported conflicting results. A 2020 population-based cohort study demonstrated a significant association between newly initiated palliative care and less health care use, including the rates of ED use, hospitalization, and intensive care unit admission.[62] Other research that examined the association between palliative care and various measures of health care use in noncancer illness reported varying results.[7,31,32,34-36,40,43-45,48,50,51,56] There 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.[7,13,14] These reviews were unable to perform other meta-analyses for outcomes that relate to the provision of high-value end-of-life care,[63] such as health care use and advanced care planning, due to limitations in the available evidence at the time. The subsequent publication of 10 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[7] in their review.[29-32,37,38,50,52,54,57] The present study provides updated evidence regarding associations of palliative care interventions with important health care use and patient-focused outcomes, specifically in patients with noncancer illness.

The lack of association with palliative care and higher QOL was unexpected. This result may be related to significant heterogeneity in the interventions between trials and the substantial influence of the study by Van Spall et al[29] on the outcome, which was found to be at high risk of bias. There was a clinically meaningful association between palliative care and higher disease-generic measures of QOL when the analysis was restricted to studies at low risk of bias, which excluded the study by Van Spall et al.[29] This finding may be related to specific differences in incremental benefits between specialist and nonspecialist palliative care interventions. Van Spall et al[29] employed a nonspecialist palliative care intervention. Differences in important outcomes between specialist and nonspecialist palliative care interventions were consistently demonstrated in the current study and in others.[61] It is also possible that the standard of "usual care" is incorporating more principles of palliative care over time, leading to smaller

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differences in nonspecialist palliative care interventions with more recently published studies, such as the study by Van Spall et al.[29] Alternatively, the findings may be due to challenges in dealing with a high burden of palliative care needs related to increased health care use, worse functional impairments, and higher levels of anxiety and depression in these patients compared with patients with cancer.[64-66]

Limitations

This study has several limitations. First, it excluded other important but far less prevalent conditions, such as neurodegenerative disorders (eg, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis), other chronic lung diseases (eg, pulmonary fibrosis), rheumatologic diseases (eg, systemic sclerosis, lupus, rheumatoid arthritis), and HIV/AIDS. Second, some trials of mixed disease included a minority of patients with cancer, which may have influenced the findings. However, sensitivity analyses that specifically excluded trials with some patients with cancer revealed findings consistent with 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. Because 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.[7] Consequently, the results suggest that the expansion of generalist palliative care programs in large health care systems may be beneficial given that the current demand for palliative care has outstripped the supply of specialized palliative care clinicians.[67] However, this study, and prior work, has demonstrated additional benefit when care is provided by specialist palliative care clinicians.[61,68] 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 health care 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.[69] Seventh, the potential relationship between the presence of advance care planning and the other study outcomes was not evaluated because this outcome 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.[25,26] This may be especially relevant because patients with noncancer illness are more likely to receive palliative care closer to death than patients with cancer, and the timing of a shift from curative treatment strategies to comfort care is less clear.[10,62]

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 health care use and modestly lower symptom burden, but there was no significant difference in QOL. Analyses for some outcomes were based predominantly on studies of patients with HF, which may limit generalizability to other chronic illnesses.

ARTICLE INFORMATION

Accepted for Publication: July 16, 2020.

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Critical revision of the manuscript for important intellectual content: Quinn, Shurrab, Gitau, Kavalieratos, Isenberg, Stall, Stukel, Goldman, Detsky, Bell.
Statistical analysis: Quinn, Shurrab, Stall, Stukel.
Obtained funding: Quinn.
Administrative, technical, or material support: Quinn, Gitau, Kavalieratos, Isenberg, Stall, Horn.
Supervision: Kavalieratos, Goldman, Cram, Detsky, Bell.

Conflict of Interest Disclosures: Dr Kavalieratos reported receiving grants from the National Heart, Lung, and Blood Institute during the conduct of the study. Dr Cram reported receiving grants from the National Institutes of Health outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the Sinai Health System Research Foundation. Drs Quinn and Stall receive funding from the Canadian Institutes of Health Research Vanier Scholarship Program, the Eliot Phillipson Clinician-Scientist Training Program, and the Clinician Investigator Program at the University of Toronto. Dr Kavalieratos receives research funding from the National Institutes of Health (K01HL133466), the Cystic Fibrosis Foundation, and the Milbank Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Additional Contributions: We thank Juan Diaz Martinez, MSc (Biostatistics Research Unit, University Health Network, University of Toronto), for his assistance with the statistical analyses and creation of the figures. He was not compensated for his contribution.

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