


ORIGINAL RESEARCH

Palliative Care Consultation Reduces Heart Failure Transitions: A Matched Analysis

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BACKGROUND: Palliative care supports quality of life, symptom control, and goal setting in heart failure (HF) patients. Unlike hospice, palliative care does not restrict life-prolonging therapy. This study examined the association between palliative care during hospitalization for HF on the subsequent transitions and procedures.

METHODS AND RESULTS: Veterans admitted to hospitals with HF from 2010 to 2015 were randomly selected for the Veterans Administration External Peer Review Program. Variables pertaining to demographic, clinical, laboratory, and usage were captured from Veterans Administration electronic records. Patients receiving hospice services before admission were excluded. Patients who received palliative care were propensity matched to those who did not. The primary outcomes were whether the patient experienced transitions or procedures in the 6 months after admission. Transitions included multiple readmissions (≥ 2) or intensive care admissions and procedures included mechanical ventilation, pacemaker implantation, or defibrillator implantation. Among 57 182 hospitalized HF patients, 1431 received palliative care, and were well matched to 1431 without (standardized mean differences $\leq \pm 0.05$ on all matched variables). Palliative care was associated with significantly fewer multiple rehospitalizations (30.9% versus 40.3%, $P < 0.001$), mechanical ventilation (2.8% versus 5.4%, $P = 0.004$), and defibrillator implantation (2.1% versus 3.6%, $P = 0.01$). After adjustment for facility fixed effects, palliative care consultation was associated with a significantly reduced hazard of multiple readmissions (adjusted hazard ratio = 0.73, 95% CI, 0.64–0.84) and mechanical ventilation (adjusted hazard ratio = 0.76, 95% CI, 0.67–0.87).

CONCLUSIONS: Palliative care during HF admissions was associated with fewer readmissions and less mechanical ventilation. When available, engagement of HF patients and caregivers in palliative care for symptom control, quality of life, and goals of care discussions may be associated with reduced rehospitalizations and mechanical ventilation.

Key Words: hospice ■ palliative care ■ readmission

As heart failure (HF) progresses, patients experience high symptom burden that negatively impacts function, creates suffering, and increases mortality.¹ By 2030, the prevalence of HF will grow by 46%, resulting in >8 million adults living with the condition, and an estimated \$69.7 billion in total costs.² Palliative care has become recognized as a beneficial component of HF management, particularly for symptom management and quality of life.^{3–5} The 2013 American College of Cardiology Foundation/American

Heart Association Guideline for the Management of Heart Failure recommended palliative care for some hospitalized patients and care coordination for chronic HF.⁶ However, palliative care remains underutilized among the HF population.^{3,7,8}

Critical and holistic thinking is essential to ensure the well-being of patients with HF and their families, as well as the minimization of unnecessary healthcare usage. Palliative care focuses on improving a patient's quality of life by managing pain and other distressing

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CLINICAL PERSPECTIVE

What Is New?

- The multidisciplinary approach of palliative care includes interventions aimed at minimizing suffering and maximizing quality of life in heart failure patients without the need to forgo life-prolonging care as in hospice.
- This analysis found that palliative care consultation during heart failure hospitalization reduced transitions, which included ≥ 2 rehospitalizations, and procedures such as mechanical ventilation.

What Are the Clinical Implications?

- The availability of palliative care for heart failure patients during hospitalization may limit these outcomes.
- As health systems develop population health approaches to delivery of care, palliative care for heart failure patients could be considered as an adjunct to improve patient quality of life, symptom management, and goal setting.

Nonstandard Abbreviations and Acronyms

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
AICD	automated implantable cardiac defibrillator
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
HF	heart failure
HR	hazard ratio
ICD-9	<i>International Classification of Diseases, Ninth Revision</i>
ICU	intensive care unit
LOS	length of stay
SMD	standard mean difference
VA EPRP	Veterans Administration External Peer Review Program
VAMC	Veterans Affairs Medical Center
VA	Veterans Administration

symptoms of a serious illness. Palliative care can be provided concurrent with other medical treatments.⁹ The multidisciplinary approach of palliative care includes interventions aimed at minimizing suffering and maximizing quality of life.

Understanding the association of palliative care with transitions and procedures for patients living with HF can provide important insights into the use of palliative care. In other function-limiting and life-limiting conditions, such as terminal cancer and advanced cognitive impairment, outcomes have centered on repeat transitions in care settings or procedures such as intensive care unit admission, mechanical ventilation, or feeding tube insertion.¹⁰⁻¹² In the HF population, inclusion of additional procedures, such as cardiac surgery or placement of a pacemaker or defibrillator, may be important markers.¹³

This retrospective, propensity-score matched cohort study examined the association of palliative care engagement during HF hospitalization with transitions and procedures. The study's hypothesis was that among patients admitted to the hospital with HF, palliative care services would be associated with fewer transitions and procedures in the 6 months after hospitalization than a matched HF cohort who did not receive palliative care.

METHODS

Data Availability

Based on restrictions in the Data Use Agreements used in this study, the authors are unable to make a data set available. Methodology questions may be directed to the corresponding author.

Study Design

This retrospective propensity-matched analysis identified HF admissions from the Veterans Administration External Peer Review Program, which randomly selected medical records for review related to quality and performance during hospitalization. Trained nurses reviewed the selected records for data on performance and exclusionary conditions.¹⁴ The External Peer Review Program cohort used for this analysis included patients admitted with heart failure from October 2009 to September 2015. In the case of multiple readmissions, the analysis focused on the first readmission (index admission). Patients on hospice before admission as defined by Veterans Administration (VA) or Medicare records were excluded. A total of 124 Veterans Affairs Medical Center acute care hospitals were included.

Ethics

Before data collection, Institutional Review Board approval was obtained from the Providence Veterans Affairs Medical Center. This retrospective study was performed on clinically collected data and informed consent was waived.

Main Exposure: Palliative Care Encounter

Palliative care was operationalized as at least 1 hospital medical encounter with a palliative care professional occurring between the admission date and 3 days after the discharge. Within the VA, hospital encounters can be completed after discharge because care coordination is non-billable and attached to the initial encounter. Encounters were included for up to 3 days after the discharge date. The VA uses this method of encounter measurement for workload capture.

To exclude patients who had hospice before admission, usage was examined in the year before the admission date from VA encounters, VA billing records for hospice services, and Medicare records for hospice care.

Outcomes

The primary outcome of interest was transitions and procedures 6 months after discharge. Using VA and Medicare records, we identified the number of hospitalizations after discharge, intensive care unit admissions, and hospice enrollments. Procedures were captured with *International Classification of Diseases, Ninth Revision (ICD-9)* procedure codes after the initial palliative care encounter and included mechanical ventilation, pacemaker placement, automated cardiac defibrillator placement, cardiac surgery including coronary bypass or valve replacement, and insertion of a feeding tube.

Covariates for Propensity Matching

From the VA data infrastructure, demographics such as age, sex, and race were identified for each patient. In addition, comorbidity data were gathered to complete the Elixhauser comorbidity index from the year before admission based on VA encounter coding. Vital signs, laboratory, and ejection fraction data were included from the admission of interest. Laboratory variables used for the analysis were prioritized on the nearest proximity to the time of admission. Not all patients had an echocardiogram during the admission of interest. If the ejection fraction was not available from the admission of interest, data were extrapolated 6 months before or after the admission. Prior-year VA costs and hospital days were included as matching variables. Prior work found that prior year VA costs helped to account for unobserved variance.¹⁵ To address potential mismatch in exposure to the composite outcome, days alive after hospitalization was included in the propensity matching.

Facility Palliative Care Availability

To address variation among VA hospitals in the availability of palliative care that could be correlated with

other practice patterns, we also controlled for facility effects in the percentage of HF admissions with palliative care encounters (Figure S1).

Missing Data

Missing data were rare with respect to demographic information. Comorbidities were scored as present if the code was used within the prior year. For laboratory and clinical data, multiple imputations were used if the information was not present in the VA medical record. A listing of matching variables is included in Table S1.

Statistical Analysis

We estimated propensity scores using a logistic model of palliative care on patient covariates. Covariates were maintained as continuous during the matching. Patients in the palliative care cohort were matched on a 1:1 ratio to those in the non-palliative-care cohort using greedy, nearest-neighbor matching with a radius of 0.01 and without replacement. The standardized mean difference was examined to assess covariate balance. Past literature found a mean standardized difference of <0.20 appropriate for suitable matching on variables.¹⁶

We analyzed transitions and procedures in the matched sample in 3 ways. In the first analysis, the outcome was operationalized as the proportion of patients having a transition or procedure within 6 months after admission. Proportions were compared using Chi-square statistics. The second analysis examined time until the first transition or procedure. A Cox proportional hazard model was used to adjust residual mortality risk and to censor for death.¹⁷ To confirm that death is a competing risk in the model, the cause-specific hazard model, as well as, the sub-distribution hazard model were developed and yielded similar results.¹⁸ A third model included adjustment for facility availability of palliative care for HF as a fixed effect. Kaplan–Meier curves were created from the time of discharge to the outcome and compared with a log-rank test.

RESULTS

Baseline Characteristics

Table 1 describes the admitted (n=58 712), the palliative care (n=1431), and the matched (n=1431) cohorts. There were significant measurable differences between the overall cohort and the palliative cohort with respect to age, comorbidity, clinical data, prior usage, cost, and mortality. The palliative cohort was older with more comorbidity, lower ejection fraction, more days in the hospital, more costs, and higher post-hospitalization

Table 1. Comparison of the Matched Cohorts

	Admitted Cohort n=58 712	Palliative Cohort n=1431	Matched Cohort n=1431	Standardized Difference*	
	Mean (SD) or % (n)	Mean (SD) or % (n)	Mean (SD) or % (n)	Palliative vs Matched	Palliative vs Admitted
Demographics					
Age, y	70.85 (11.39)	75.84 (11.14)	75.70 (11.02)	0.01	0.44
Men	98.15 (57 626)	98.67 (1412)	98.60 (1411)	0.01	0.04
Race				0.00	0.15
White	74.77 (43 897)	80.57 (1153)	80.92 (1158)		
Black	23.39 (13 730)	18.03 (258)	17.96 (257)		
Other	1.85 (1085)	1.40 (20)	1.12 (16)		
Comorbidities					
MI	22.08 (12 965)	29.91 (428)	30.89 (442)	-0.02	0.18
Diabetes mellitus	54.06 (31 741)	50.73 (726)	49.34 (706)	0.03	-0.07
Lymphoma	1.73 (1017)	2.24 (32)	1.75 (25)	0.04	0.04
Solid tumor	13.70 (8042)	18.94 (271)	18.52 (265)	0.01	0.14
Metastatic disease	1.38 (812)	4.05 (58)	3.42 (49)	0.03	0.16
Elixhauser	5.43 (2.86)	6.26 (2.98)	6.25 (2.88)	0.01	0.29
Laboratory data					
Renal function					
Blood urea nitrogen	26.63 (14.13)	32.49 (15.58)	32.75 (16.85)	-0.02	0.39
Creatinine	1.54 (0.87)	1.71 (0.90)	1.73 (0.99)	-0.02	0.19
Sodium	138.50 (3.97)	138.06 (4.67)	138.11 (4.20)	-0.01	-0.10
Brain natriuretic peptide	1415 (1292)	1753 (1479)	1750 (1601)	0.00	0.24
Potassium	4.17 (0.54)	4.25 (0.59)	4.24 (0.56)	0.01	0.13
Hematocrit	37.09 (6.09)	36.22 (6.32)	35.89 (6.03)	0.05	-0.14
Clinical data					
Ejection fraction	40.19 (16.28)	36.96 (17.40)	36.81 (15.90)	0.01	-0.19
Blood pressure (mean arterial)	97.78 (15.32)	92.06 (14.51)	91.64 (15.09)	0.03	-0.38
Pulse	80.80 (16.79)	81.92 (17.18)	81.77 (16.49)	0.01	0.07
Body mass index	31.45 (7.52)	29.34 (6.96)	29.20 (6.71)	0.02	-0.29
Usage data					
Hospitalizations in prior 12 mo (mean, n)	1.06 (1.50)	1.62 (2.02)	1.39 (1.69)	0.12	0.31
Mean hospitalization length in prior 12 mo, d	7.70 (22.99)	10.43 (22.37)	9.88 (25.25)	0.02	0.12
Days alive after index admission	1183 (865)	553 (629)	553 (608)	0.00	-0.83
Death in 6 mo after index admission	14.54 (8535)	39.90 (571)	37.88 (542)	0.04	0.59
Baseline cost					
Total cost in prior 12 mo	32 729 (47 040)	43 363 (53 359)	42 076 (57 756)	0.02	0.21

MI indicates myocardial infarction.

*The standardized difference is the difference of the group means divided by the standard deviation of the cohort.

mortality rates. Propensity analysis was used to obtain a comparison cohort and the propensity matching reduced the standard mean difference (SMD) to <0.20 in all matched variables. Both the palliative and matched cohorts were older (75.8 versus 75.7 years, SMD 0.01), mostly men (98.7% versus 98.6%, SMD 0.01), and had multiple comorbid conditions as determined by the mean Elixhauser comorbidity index (6.3 versus 6.3, SMD 0.01). The palliative and matched cohorts accrued significant medical costs in the year

before index admission (\$43 363 versus \$42 076, SMD 0.02), respectively. Overall, 39.9% of the palliative care cohort had died within 6 months of discharge compared with 37.9% of the matched cohort (SMD 0.04).

Outcomes

Transitions and procedures within 6 months of discharge are displayed in Table 2. The palliative care cohort was associated with fewer multiple readmissions

Table 2. Transitions and Procedures in the Matched Cohorts

	Palliative Care Cohort n=1431		Matched Cohort n=1431		P Value
	n	%	n	%	
Transitions					
Intensive care unit admission	227	15.9	255	17.8	0.1619
Readmission (n≥2)	442	30.9	577	40.3	<0.0001
Hospice admission	498	34.8	262	18.3	<0.0001
Procedures					
Mechanical ventilation	40	2.8	78	5.4	0.0004
Pacemaker	6	0.4	6	0.4	1.0000
Defibrillator implantation	30	2.1	52	3.6	0.0137
Cardiac surgery	7	0.5	11	0.8	0.3443
Hemodialysis	49	3.42	64	4.47	0.1499
Feeding tube	6	0.4	7	0.5	0.7810

(2+ readmissions) compared with the matched cohort (30.9% versus 40.3%, $P<0.001$). There was no statistically significant difference in intensive care unit admission (15.9% versus 17.8%, $P=0.162$). Compared with the matched cohort, the palliative cohort had less mechanical ventilation (2.8% versus 5.4%, $P=0.004$). Palliative care was associated with lower automated implantable cardiac defibrillator placement (2.1% versus 3.6%, $P=0.01$) but no difference in pacemaker placement (0.4% versus 0.4%, $P=1.0$), cardiac surgery (0.5% versus 0.8%, $P=0.34$), or hemodialysis (3.4% versus 4.5%, $P=0.15$). Our secondary outcome of hospice use in the 6 months after discharge was significantly higher in the palliative cohort (34.8% versus 18.3%, $P<0.001$).

Table 3 describes the results of the proportional hazard model which found a significant 25% reduction in the hazard of the multiple readmissions (≥ 2) outcome in the palliative care cohort (hazard ratio [HR] 0.76, 95% CI, 0.68–0.85) with censoring for death during the 6-month follow-up. Inclusion of the facility availability of palliative care as a fixed effect in the analysis did not significantly alter the results (adjusted HR 0.73, 95% CI, 0.64–0.84). Palliative care was similarly associated with a decline in the hazard of mechanical ventilation after adjusting for facility fixed effects (adjusted HR 0.76, 95% CI, 0.67–0.87). Figure illustrates

the association of palliative care and the comparison group for the multiple readmissions (Figure A) and mechanical ventilation (Figure B) outcomes over the follow-up period.

Patients who received palliative care were more likely to receive palliative care on a subsequent hospitalization (14.4% versus 8.3%, $P<0.001$) or during an outpatient encounter (20.6% versus 3.4%, $P<0.001$).

DISCUSSION

Past evidence supports palliative care as an effective intervention for improving quality of life in HF.^{19–21} The cohort with palliative care was older with more comorbidity, usage, and cost in the prior year, necessitating the use of a propensity-score matched comparison cohort. Using this propensity-score matched cohort, we found that palliative care consultation during admission for HF was associated with fewer rehospitalizations and increased enrollment in hospice in the 6 months after hospitalization. These findings add to an increasing number of analyses that found associations between palliative care and positive outcomes for patients experiencing HF.

Palliative care is one additional service cardiologists can use in their comprehensive management of patients with HF. The observed association with reduced rehospitalization within 6 months among patients who received palliative care provides additional support that a palliative approach may be used to help guide goals of care conversations with patients living with HF. Also, engagement of palliative care during hospitalization may build an ongoing relationship that increases palliative care and facilitates discussion during subsequent hospitalizations or outpatient visits. Prior evidence suggests that palliative care might reduce healthcare costs.^{22–25} When allowed, palliative care may be used concurrently with curative, life-preserving treatment. For this analysis, patients in the palliative care cohort still opted for procedures such as hemodialysis and defibrillator implantation.

Prior outcomes of palliative care studies, developed in dementia and oncology research^{11,12,26} focused on similar outcomes (Table S2). In the HF population, other care procedures, such as implantation of an automated cardiac defibrillator, pacemaker, or cardiac surgery, have strong evidence in advanced HF. However,

Table 3. Hazard Ratios of Palliative vs Control for Transitions and Procedures Within 180 Days of Discharge

Transition	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR With Facility Fixed Effects (95% CI)*
Readmissions (n≥2)	0.76 (0.68–0.85)	0.70 (0.62–0.79)	0.73 (0.64–0.84)
Mechanical ventilation	0.79 (0.71–0.88)	0.77 (0.69–0.86)	0.76 (0.67–0.87)

HR indicates hazard ratio.

*Adjusted for mortality risk and censored for death.

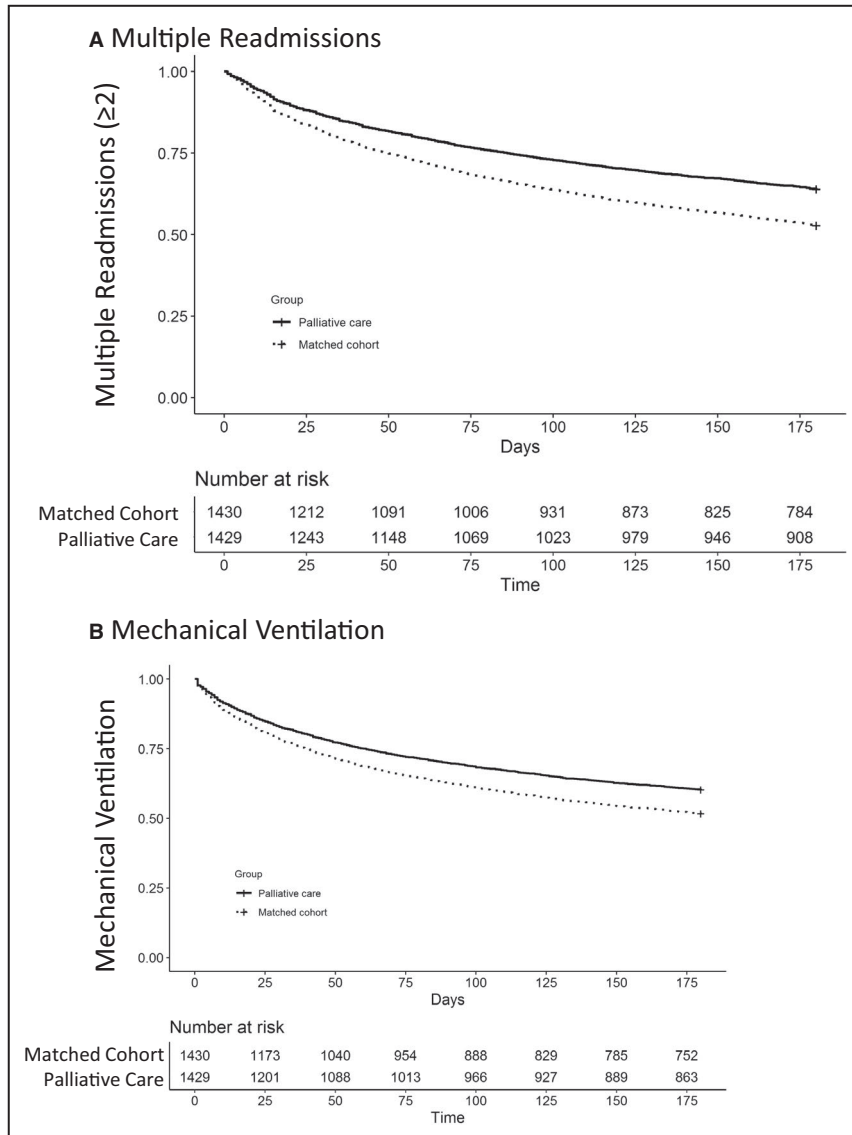


Figure. Kaplan–Meier curve for multiple readmissions and mechanical ventilation. For the 180-day follow-up period, cohorts were tracked for first occurrence of multiple readmissions (A) and mechanical ventilation (B). The population at risk after censoring for death and outcome is described in the tables below the curves. In both panels, palliative care was significantly different than the matched cohort ($P < 0.001$).

HF is a progressive disease with increasing symptom severity and functional decline. This decline in function, while on a different trajectory than dementia and oncology, is challenging for HF patients. Palliative care brings an opportunity to individualize care management toward the patient’s goals through goals of care conversations, symptom management, or continuity across settings.

Importantly, palliative care is not universally available. In this study, we found a wide variability in the palliative care encounters for patients hospitalized with HF among medical centers (Figure S2). We postulate that palliative care is underutilized in part because of the misconception that it is synonymous

with hospice.^{7,27,28} While both hospice and palliative care focus on symptom control, hospice enrolls patients who meet reimbursement eligibility criteria (a life expectancy of <6 months) and cannot be provided concurrently with curative treatment for the terminal condition. Palliative care and hospice can be provided wherever a patient resides (eg, home, hospice center, hospital, long-term care facility, etc).⁹ In an integrated system such as the VA, palliative care can be delivered concurrently with more aggressive HF therapy.²⁹ Palliative care uses a shared decision-making strategy, which is influenced by a complex interplay among patient, family, provider, and systemic factors.^{30–33} Prior work found that

this approach is associated with a decrease in HF symptoms, increased satisfaction, reduced cost, and reduced transitions.^{24,25,34} With similar mortality between the groups, the stark difference in hospice enrollment between the palliative and matched cohorts demonstrates that the palliative approach may increase hospice referral and suggests that there is an HF population with an unmet need who may benefit from the additional layers of support that concurrent palliative care offers.

Strengths

This is a large study representing >58 000 patients. The study population represents patients from Veterans Affairs Medical Centers across the United States, allowing for geographic and racial diversity. The palliative cohort was successfully matched on a 1:1 ratio and the non-palliative care cohort and multiple data sources were combined to provide comprehensive measurement of transitions and procedures in the cohort. These data sources were also used to exclude patients on hospice before HF admission and to measure the transition to hospice after admission which is critical to examine the impact of concurrent palliative care and HF care.

Limitations

Propensity matching is challenging for patients with palliative care, as there is a degree of unmeasured confounding in the selection of patients who receive palliative care. As with all matched cohort analyses, we were unable to demonstrate a causal relationship with this analysis. Other limitations of this study are related to the available sample. The population demographics and the availability of the data in the electronic medical record limit generalizability to the VA healthcare system, given the patients were predominantly male Veterans and there was no external validation. Additionally, the availability of concurrent palliative care and HF care is limited in health systems that are not integrated. Our data did not comment on critical components of end-of-life care such as functional status, quality of life, and caregiver support, as these variables were not available in the electronic medical record.

CONCLUSIONS

This study demonstrated an association between palliative care services in admitted HF patients and reduced multiple readmissions and mechanical ventilation. As HF progression is characterized by progressive functional decline, there is a growing understanding that concurrent palliative care can play an important role in attenuating the impact of HF, controlling symptoms, and providing continuity of care to meet the patients' goals.

Translational Outlook

The symptoms and progression of HF lead to a decline in functional abilities. Palliative care has become increasingly recognized as a beneficial component of HF management, particularly in improving symptoms and quality of life. In patients admitted to the hospital with HF, this study found that palliative care was associated with less multiple rehospitalizations and mechanical ventilation. However, palliative care was not available at all medical centers. Targeted collaborations and increasing the palliative care workforce will be critical to meeting the growing HF demand.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1 and S2
Figures S1 and S2

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Supplemental Material

Table S1. Missing Data from Variables Included in the Propensity Matching.

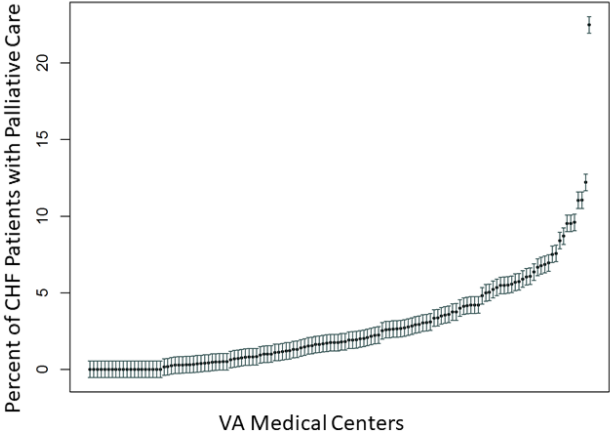
Missingness Table	Palliative Cohort		Matched Cohort	
	N=1431		N=1431	
	Nonmissing N	Missing % (N)	Nonmissing N	Missing % (N)
Demographics				
Age	1431	0% (0)	1431	0% (0)
Sex	1431	0% (0)	1431	0% (0)
Race	1431	0.7% (10)	1419	0.8% (12)
Elixhauser Comorbidity	1431	0% (0)	1431	0% (0)
Laboratory Data				
Urea Nitrogen (BUN)	1286	10.1% (145)	1330	7.1% (101)
Creatinine	1306	8.7% (125)	1303	8.9% (128)
Sodium	1377	3.8% (54)	1382	3.4% (49)
Brain Naturetic Peptide (BNP)	892	37.7(539)	931	34.9(500)
Potassium	1343	6.2% (88)	1373	4.1% (58)
Hematocrit	1341	6.3% (90)	1375	3.9% (56)
Clinical Data				
Ejection Fraction	1428	0.2% (3)	1425	0.4% (6)
Blood Pressure (Mean Arterial)	1400	2.2% (31)	1419	0.8% (12)
Pulse	1400	2.2% (31)	1420	0.8% (11)
Body Mass Index	1176	17.8% (255)	1231	14.0% (200)
Utilization Data				
Mean LOS in prior 12 months of hospitalizations	1431	0% (0)	1431	0% (0)
Days Alive after Index Admission	1431	0% (0)	1431	0% (0)
Baseline Cost				
Total cost in prior 12 months	1431	0% (0)	1431	0% (0)

Table S2. Burdensome Transition Outcome in the HF Population.

	Palliative Cohort N=1431		Matched Cohort N=1431		p-value
	N	%	N	%	
Burdensome Transition*	516	36.1	655	45.8	<.0001

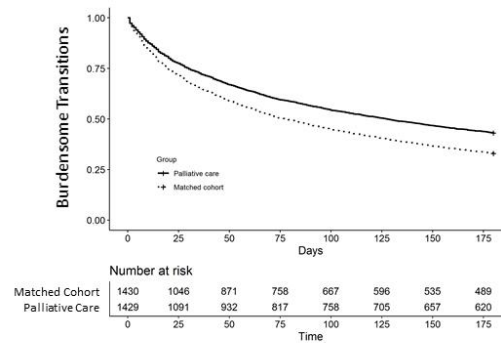
*The Burdensome Transition composite outcome includes 2+ readmissions, ICU admission, feeding tube or mechanical ventilation in the 6 months after index hospitalization; Proportional hazard modeling identified a significant reduction in the hazard of burdensome transition among those with palliative care consultation (HR = 0.78, 95%CI 0.69,0.88). After adjustment for facility fixed effects, the hazard of burdensome transition was significantly reduced in those with palliative care consultation (adjusted HR =0.75, 95%CI 0.65, 0.86)

Figure S1. Variability among VA Medical Centers in Palliative Consultation among HF Patients.



Each VA Medical Center (n=129) is represented as a point on the horizontal axis, there is a variability in the availability and utilization of palliative care among CHF patients.

Figure S2. Kaplan Meier Curve for Burdensome Transitions*.



The Burdensome Transition composite outcome includes 2+ readmissions, ICU admission, feeding tube or mechanical ventilation in the 6 months after index hospitalization; Proportional hazard modeling identified a significant reduction in the hazard of burdensome transition among those with palliative care consultation (HR = 0.78, 95%CI 0.69,0.88). After adjustment for facility fixed effects, the hazard of burdensome transition was significantly reduced in those with palliative care consultation (adjusted HR =0.75, 95%CI 0.65, 0.86)