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Factors Associated with the Place of Death in Huntington Disease: Analysis of Enroll-HD

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Abstract

Background: Most people prefer to die at home. Hospice is the standard in end-of-life care for people with Huntington disease (HD), a neurodegenerative genetic disorder that affects people in middle adulthood. Yet, we have little knowledge regarding the place of death for people with HD. Therefore, the current state of knowledge limits HD clinicians' ability to conduct high-quality goals of care conversations.
Objectives: We sought to determine the factors associated with the place of death in people with HD.
Design: We obtained cross-sectional data from Enroll-HD and included participants with a positive HD mutation of 36 or more CAG repeats.
Results: Out of 16,120 participants in the Enroll-HD study, 536 were reported as deceased. The mean age at death was 60. The leading place of death was home (29%), followed by the hospital (23%). The adjusted odds ratio (aOR) of dying at a skilled nursing facility was significantly lower for those partnered (aOR: 0.48, confidence interval [95% CI]: 0.26–0.86). The aOR for dying on hospice compared to home was increased in a person with some college and above (aOR: 2.40, 95% CI: 1.21–4.75).
Conclusions: Our data further suggest that models that predict the place of death for serious illnesses do not appear to generalize to HD. The distribution in the places of death within HD was not uniform. Our findings may assist HD clinicians in communication during goals of care conversations.

Keywords: end of life; Huntington disease; place of death

Introduction

Huntington disease (HD) is a rare neurodegenerative disease that typically manifests in middle adulthood. It causes inexorable psychiatric, motor, and cognitive deterioration, culminating with death an average of 15 years after the first abnormal motor signs manifest.[1] To date, the palliative care literature has highlighted that people with serious illnesses desire to die at home (25%–87%).[2] Prior study across multiple centers in the United States, however, has suggested

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that around 46% of people with HD, aggregated among all stages of the disease (prodromal, early, and late stage), have not even thought about their preferred place of death, despite the terminal nature of the disease and its predictable course.[3] Furthermore, investigators identified only rudimentary factors that predict institutionalization among people with HD (i.e., physical impairments).[4,5]

For other serious illnesses, such as terminal cancer, researchers developed and validated a model to predict what domains (illness, environmental, and individual) may associate with the place of death.[6] These domains have mostly recapitulated to Alzheimer's disease and related dementias (ADRD) and have provided invaluable information to assist with targeted communication efforts to achieve goal concordance.[7] However, whether this model generalizes to HD is unknown. An account of what factors relate to the place of death among people with HD would assist clinicians during serious illness conversations. Indeed, assessing these factors would provide patients and families additional insights into a personalized prognosis concerning the death and dying process, a vital patient-reported outcome (PRO) measurement recently psychometrically validated to HD.[8]

Indeed, preliminary evidence on the distribution of the place of death between ADRD, which represents more common neurodegenerative illnesses, and HD diverges. While nearly two-thirds of people with ADRD die at skilled nursing facilities (SNFs),[9] among people with HD, a European study—which did not examine factors associated with the place of death—suggests that the top place of death is the hospital (nearly 30%).[10] Clinical manifestations between these two categories of diseases might also indicate that factors related to the place of death would naturally diverge.

Therefore, given this present shortcoming in the literature and its opportunity to enhance patient-physician serious illness communication for this rare disease, we sought to perform a retrospective analysis internationally. We used an HD registry to examine what chronic illness and HD-specific factors[4,5,11] may contribute to the place of death based on the established ''variations of place of death''[6] model used in terminal cancer care. We determined whether illness (CAP score, total functional capacity [TFC]), environmental (marriage/partnership, and residence) and individual factors (race, sex, education level, and cause of death) would associate with the place of death. We hypothesized, based on a meta-analysis that conceptualized several drivers related to the place of death for other serious illnesses,[6] that the presence of partnership/marriage, male sex, and higher education level would be associated with a home death.

Methods

Study design and participants

We performed a cross-sectional analysis from Enroll-HD, an international observational registry covering 171 sites in 20 countries.[12] Qualified HD investigators, with permission, may utilize this dataset. Recruitment started in 2012 and is ongoing. The Enroll-HD database also partially merged a cohort, ''REGISTRY,'' an observational study among people with the HD mutation in Europe. REGISTRY concluded in 2015; thus, at its conclusion, participants from REGISTRY who wished to participate in HD observational research provided permission to migrate their data to Enroll-HD. We utilized the most recently available dataset, the PDS5, an electronic capture of the Enroll-HD's database from 2012 through October 2020.[13] Further information surrounding the demographics, attrition, and the measurements/procedures involved may be found elsewhere.[13]

Study variables

Qualified investigators may review Enroll-HD's data dictionary.[13] The dependent variable was the place of death. Categorical outcomes for the place of death include the hospital, home, SNF, hospice care, or other. As our study incorporates participants enrolled at North American and European sites, the designation of hospice was not separated into the home versus SNF. The Enroll-HD coordinator selects hospice without defining the setting; thus, these do not invariably imply mutually exclusive categories.

Based on a previous model for determinants of the place of death,[6] we incorporated analogous illness and environmental and individual factors available through Enroll-HD as the independent variables. Our illness-specific variables were the following: age at death, a continuous number; TFC, a continuous number; disease stage, a categorical variable; and CAP score, also a continuous number. TFC ranges from 0 to 13, with higher scores indicating greater levels of normalcy, and evaluates a participant's ability to conduct one's occupation and perform finances/chores and other activities of daily living. TFC assists in classifying participants into their respective stages of the disease.[14]

Early-stage manifesting indicates unequivocal motor signs and a TFC score that ranges from 7, inclusive, to 13, inclusive. Late-stage manifesting denotes unequivocal motor signs and a TFC score of <7. Premanifesting or prodromal suggests the lack of unequivocal motor features, as represented on the Unified Huntington Disease Rating Scale,[15] diagnostic confidence level rating of <4 with the presence of an HD mutation.

The CAP score measures disease burden, and its calculation is the age at death multiplied by (CAG repeat length minus a constant 33.66).[16] Higher scores indicate a more significant disease burden. The CAP score was primarily used for clinical trial eligibility for those with premanifesting HD to predict the probability of phenoconversion (i.e., manifesting HD) within five years. It also serves as a ''CAG-adjusted age metric.''[17] Environment-specific variables included the following: marital status and residence. Marital status included six categories: single, partnership, married, divorced, widowed, and legally separated. We collapsed and dichotomized these six categories into two: partnered/married and other, as marriage has previously been shown to protect against institutionalization in HD and serve as a factor in home deaths.[6,11] Residence included the following options: rural, village, town, and city.

We dichotomized our choices into other (village, town, and city) versus rural and chose this delineation, given the rural environment's propensity for an at-home place of death across 15 studies.[6] Individual-specific variables included the following: race, sex, and education level. Given that most people in the Enroll-HD database are Caucasian, we demarcated the race analysis into Caucasian versus Other. Sex was dichotomized into male versus female. Education level included preschool, elementary, middle, high school,

vocational, associate/bachelors/masters, or doctoral degree; we dichotomized our analysis into ''high school and below,'' which included preschool, elementary, middle, and high school; and ''college and above,'' which included associate/bachelors/masters/doctoral degree(s).

Analytical plan

Descriptive statistics were calculated for all variables of interest. Categorical variables were summarized using counts and percentages and continuous variables with means and standard deviations (SDs). Any missing value was excluded from the analyses. A separate simple multinomial logistic regression with the place of death (home as the reference) as the dependent variable and a given independent variable (e.g., CAP score) was designed to examine the relationship between the place of death and a given independent variable one at a time. Finally, a multiple multinomial logistic regression with all independent variables of interest was included in the model. Statistical analyses were conducted with Statistical Analysis System (SAS) version 9.4 (Cary, NC).

Results

Information on 536 premanifesting and manifesting HD participants was available at the place of death. We excluded 25 participants with high CAG repeats >70 ($n = 11$) or CAG repeats >28, but <36 ($n = 14$), as these data points suggest outliers in the clinical presentation of HD. Our resulting analysis, therefore, included 511 participants. Our cohort's mean (SD) age was 60.04 (SD = 13.71). Ninety-three percent of the cohort was Caucasian; 54% were male. The majority of our cohort was late-stage manifesting (70%). Additional details regarding our cohort, including missing data, may be found in Table 1. Related to the distribution of the places of death among people with HD (Table 2 and Fig. 1), 147 people died at home (29%), 117 died at the hospital (23%), 82 died at an SNF (16%), and 51 died on hospice (10%). One hundred fourteen (22%) died at an unknown place.

In our primary unadjusted analysis, disease stage, TFC, and education level were each significantly associated with the place of death. The odds of dying on hospice compared to home in participants with late-stage manifesting was 4.32 (confidence interval [95% CI]: 1.72–10.83) times higher than participants with premanifesting/early-stage manifesting. There was no significant difference in the odds of death at a hospital compared to the home in participants with late-stage manifesting compared to participants with premanifesting/early-stage manifesting.

Upon comparing the odds of death at an SNF versus home, the most significant difference was between late-stage and early-stage manifesting HD groups: the late-stage manifesting participants demonstrated a 7.63 (95% CI: 3.11–18.73) times higher odds. For each incremental value increase in the TFC, the estimated odds of dying at hospice care, a hospital, or an SNF, compared to home, increased by a factor of 0.87 (95% CI: 0.79–0.95), 0.95 (95% CI: 0.89–1.02), and 0.70 (95% CI: 0.63–0.78), respectively.

We then built a multinomial logistic regression model to adjust for potential confounding factors (Table 3). Any observation with a missing value in the CAP score, disease stage, marital status, rural care, race, sex, and education level was discarded. The TFC was not in the multiple multinomial

TABLE 1. PATIENT DEMOGRAPHICS BY PLACE OF DEATH

		Place of death				
	Overall N = 511	*Home* N = 147	*Hospital* N = 117	*Nursing home* N = 82	*Hospice* N = 51	*Unknown* N = 114
Variable of interest	*N* (%)/mean(SD)	*N* (%)/mean (SD)	*N* (%)/mean (SD)	*N* (%)/mean (SD)	*N* (%)/mean (SD)	*N* (%)/mean (SD)
Age of death[a]	60.04 (13.71)	59.32 (13.42)	57.97 (14.90)	62.73 (12.14)	59.35 (14.50)	61.44 (13.29)
Research larger CAG allele determined from DNA	43.83 (4.43)	43.76 (4.17)	44.54 (5.35)	43.61 (3.22)	44.59 (5.97)	43.02 (3.48)
CAP score = AGE × (CAG −33.66)[a]	565.67 (125.84)	557.53 (108.16)	569.06 (123.96)	593.45 (98.47)	578.10 (145.72)	547.08 (152.07)
Total functional capacity	4.60 (3.81)	5.46 (3.83)	4.74 (3.82)	1.94 (2.63)	3.59 (2.84)	5.71 (3.91)
Late-manifesting disease stage	356 (69.67)	88 (59.86)	80 (68.38)	76 (92.68)	43 (84.31)	69 (60.53)
Married or partnership[a]	282 (55.29)	92 (62.59)	67 (57.26)	35 (43.21)	29 (56.86)	59 (51.75)
Live in rural area[a]	26 (5.11)	12 (8.16)	8 (6.84)	0 (0.00)	1 (1.96)	5 (4.42)
White	475 (92.95)	133 (90.48)	110 (94.02)	74 (90.24)	48 (94.12)	110 (96.49)
Male	274 (53.62)	78 (53.06)	69 (58.97)	49 (59.76)	23 (45.10)	55 (48.25)
Some college and above[a]	230 (45.73)	66 (44.90)	46 (40.71)	29 (36.25)	31 (60.78)	58 (51.79)

[a]1 missing in age of death, CAP score, marital status; 2 missing in living area; 8 missing education level.

Table 2. Place of Death by Disease Stage

Overall, N *(%)*	*All* *511*	*Disease stage*	
		Premanifesting/early-stage manifesting *155 (30)*	*Late-stage manifesting* *356 (70)*
Place of death			
Home, *N* (%)	147 (29)	59 (38)	88 (25)
Hospital, *N* (%)	117 (23)	37 (24)	80 (23)
Nursing home, *N* (%)	82 (16)	6 (4)	76 (21)
Hospice, *N* (%)	51 (10)	8 (5)	43 (12)
Unknown, *N* (%)	114 (22)	45 (29)	69 (19)

logistic regression model since TFC is co-linear with the disease stage. The total sample size for our model was 478, and only 1.85% of data were discarded (the total sample size for the original dataset was 487 (487 − 478)/487). Since we only had 1.85% missing values, we decided not to proceed with multiple imputations.

After multiple multinomial logistic regression, disease stage, marital status, education level, and race were still associated with the place of death. Two salient results emerged from this analysis. First, the adjusted odds ratio (aOR) of dying at SNF was significantly reduced for people with HD who were married/partner versus other (aOR: 0.48, 95% CI: 0.26–0.86). Second, the aOR of dying in hospice compared to home in someone with some college and above was 2.40 (95% CI: 1.21–4.75).

Discussion

Our report provides a subsequent analysis of the places of death among people with the HD mutation. To our knowledge, it is the first to identify the factors associated with each. In our cohort, the top place of death was the home, followed by the hospital, and then the SNF. These data suggest that the SNF is *not* the principal place of death for HD patients participating in these longitudinal observational studies. This result differs from similar studies in people with ADRD, in which SNFs remain the principal place of death.[7]

These differences may also reflect how death at the hospital is defined in different localities. For example, a hospital among some European cohorts refers to a rehabilitation facility (which might colloquially be referred to as an SNF in America). No method exists in either REGISTRY or Enroll-HD insofar as to how best to account for these potentially different nomenclatures. In addition, Enroll-HD represents a convenience sample whose focus is the recruitment of people with early-stage HD. Participants are likely lost to follow-up from the study before entering the latest stage of the disease, so the Enroll-HD sample is likely weighted toward people still living at home.

Previous work from our European colleagues, who examined the place of death using the REGISTRY study, indicated identifying factors associated with the place of death

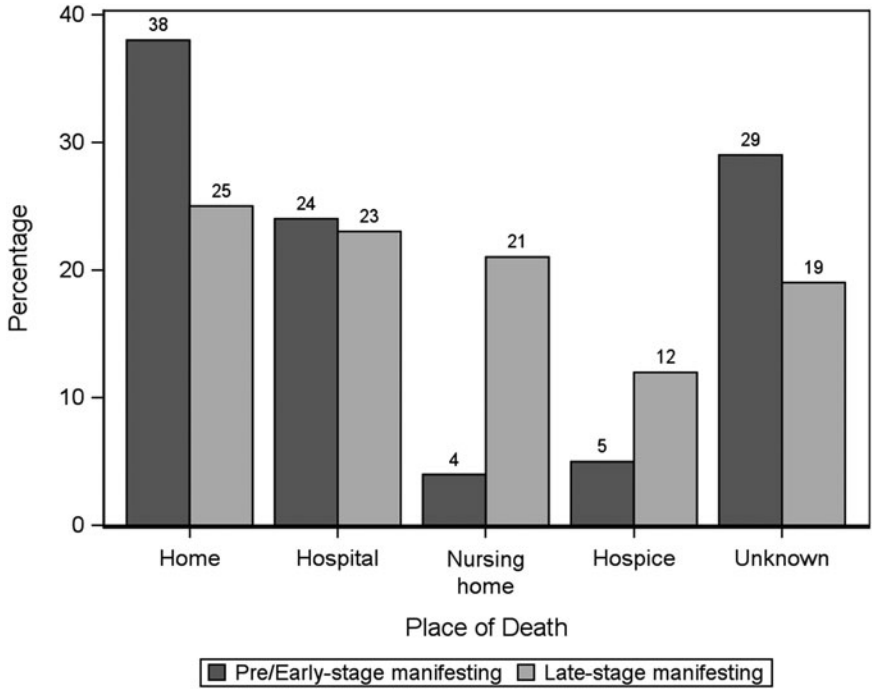

FIG. 1. Place of death by disease stage.

Table 3. Adjusted Odds Ratio and Corresponding 95% Confidence Interval for the 100 th Place of Death by Variables of Interest

	Hospice	*Hospital*	*Nursing home*	*Unknown*
Overall, N = *478*	*Adjusted OR [95% CI]*	*Adjusted OR [95% CI]*	*Adjusted OR [95% CI]*	*Adjusted OR [95% CI]*
CAP Score (per unit)	1.00 [0.10 to 1.00]	0.10 [0.10 to 1.00]	1.00 [0.10 to 1.00]	0.10 [0.10 to 1.00]
Late-stage manifesting vs. premanifesting/ early-stage manifesting (ref.)[a]	**5.07 [1.94 to 13.22]**	1.51 [0.84 to 2.70]	**8.05 [3.16 to 20.47]**	1.24 [0.70 to 2.20]
Married/partnership vs. other (ref.)	0.66 [0.33 to 1.32]	0.90 [0.53 to 1.53]	**0.48 [0.26 to 0.86]**	**0.59 [0.35 to 0.10]**
Living at rural vs. village/town/ city (ref.)	0.20 [0.02 to 1.58]	0.68 [0.26 to 1.81]	<0.00 [<0.00 to >999.99]	0.52 [0.17 to 1.55]
White vs. non-White (ref.)	1.91 [0.49 to 7.41]	1.85 [0.67 to 5.13]	1.25 [0.45 to 3.53]	**3.28 [1.02 to 10.60]**
Male vs. female (ref.)	0.79 [0.40 to 1.56]	1.22 [0.72 to 2.05]	1.43 [0.79 to 2.59]	0.69 [0.41 to 1.17]
Some college and above vs. high school and below (ref.)	**2.40 [1.21 to 4.75]**	0.91 [0.54 to 1.54]	0.89 [0.49 to 1.61]	1.56 [0.93 to 2.63]

Reference/comparator for place of death is the *home*.
Bold indicates statistical signficance.
[a]Only look at late-stage manifesting and premanifesting/early-stage manifesting.
CI, confidence interval; OR, odds ratio.

as an important future goal.[10] We, therefore, set out to identify them in this study. Except for marriage as a factor related to home death and a protector against institutionalization,[11] our data indicate that not all analogous cancer/ADRD individual, illness, and environmental factors associated with place of death generalized to HD, in contrast to our original hypotheses.

In particular, the ''variations of place of death'' model posited that two illness-specific factors (low functional status and disease duration) were associated with home death. In contrast, these analogous factors in our cohort were *not* related to home death in HD. Poor functional capacity was associated with the place of death at an SNF, not home. We even analyzed markers of functional capacity using three corelated variables. We used the TFC, treating it as a continuous measurement, and the disease stage, which binned two categories of disease stage.

Each variable demonstrated a higher OR of death at an SNF. Past work in HD suggests that poor functional status and cognitive impairments predict institutionalization.[4,5] While poor functional capacity and duration of illness relate to home as the place of death among other chronic diseases, these factors appear to preclude home as the place of death in HD. These differences may reflect our population's overwhelming motor and cognitive disabilities, which are distinct from cancer and ADRD populations, and thus deserve further study.

Additional factors countering our initial hypotheses included the participant's sex and home environment location. Notably, the rural environment demonstrated no association with the place of death, whereas it was strongly associated with home death in other cancer illnesses. Based on our experiences, we anticipated that sex would be associated with differences in the place of death. We hypothesized that this partly reflected behavior and family dynamics, which were unavailable for use in our dataset. However, neither of these variables was associated with the bivariate or multivariate models.

The primary strengths of this study are its large sample size and the certainty of the diagnosis of HD. Limitations included the relatively restricted data available, including a lack of socioeconomic data that might influence the described relationships. Our data could potentially reflect an ascertainment bias, including participants who have the resources (e.g., geographic location in a high-population area) to participate in Enroll-HD that others with HD may lack. However, we were unable to account for that information in our analysis. In addition, previous studies in other disease cohorts have suggested that patient preference is a vital driver of the place of death. However, Enroll-HD does not include information on advance care planning.

Finally, a significant limitation worth highlighting, which limits the broader interpretation of our study, surrounds a lack of study into what elements govern a dignified death to the person with HD and their family members.[18] The general public, independent of disease, perceives home as the place to receive dignified end-of-life care in survey-based studies.[19] However, the sole focus on prioritizing a particular place of death, such as the home, to the subservience of other considerations, such as addressing and treating caregiver bereavement and complex pain control,[20] may distract from the larger question of how to achieve a peaceful death in this population.[19]

Home suggests an environment, or rather a means (i.e., setting) to an end (i.e., peaceful death). However, we argue that the environment is neither necessary nor sufficient to achieve a high-quality death in this population. Instead, other factors for this population, including managing complex symptoms—which may require hospitalization or in-patient hospice use—may predominate.

Therefore, future work should explore what constitutes a high-quality death among HD stakeholders using qualitative and quantitative methods. Observational studies should also be designed to analyze caregiver and patient preferences regarding the place and cause of death in HD. In addition, data in our analysis lacked HD-validated health-related quality of

life (HRQoL) patient-reported outcomes,[8,21–23] especially palliative ones, caregiver, financial.[24] and sociodemographic metadata. These critical measurements should be collected in the future to further elucidate disparities in care and potential means to mitigate them. Indeed, those unmeasured factors may be critical determinants of resource and cost utilization in the waning years of life. Therefore, additional work is needed to examine how these factors, not measured in Enroll-HD or REGISTRY, influence end-of-life care in HD and to develop a model that explains the driving factors of the place of death in this vulnerable population.

In closing, our data suggest that different factors impact the place of death in HD, distinct from other chronic illnesses, such as cancer and ADRD. HD-neuropalliative interventions, responsive to the HRQoL PROs to this population, should be engineered and adapted from oncology and ADRD.[25] In the interim, our analysis of where people with HD die and the associated factors, or lack thereof, may assist HD clinicians throughout the end-of-life planning process.

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Authors' Contributions

L.L.S. conceived the project, wrote the first draft, devised the research questions, interpreted the work, revised the article for valuable intellectual content, and approved the final draft. All other authors oversaw the work, conception, and design, drafted the work for important intellectual content, and approved the final draft.

Ethics Approval

The Institutional Review Boards of Enroll-HD sites approved data collection.

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