End-Of-Life Discussions Reduce The Utilization of Life-Sustaining Treatments During The Last Three Months of Life in Cancer Patients : A Nationwide Population-Based Cohort Study

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Research Article

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Abstract

Purpose

Studies to examine the impact of end-of-life (EOL) discussions on the utilization of life-sustaining treatments near death were limited and had inconsistent findings. This nationwide population-based cohort study determined the impact of EOL discussions on the utilization of life-sustaining treatments in the last three months of life in Taiwanese cancer patients.

Methods

This cohort study included adult cancer patients from 2012–2018, which were confirmed by pathohistological reports. Life-sustaining treatments during the last three months of life included cardiopulmonary resuscitation, intubation, and defibrillation. EOL discussions in cancer patients were confirmed by their medical records. Association of EOL discussions with utilization of life-sustaining treatments were assessed using multiple logistic regression.

Results

Of 381,207 patients, the mean age was 70.5 years and 19.4% of the subjects utilized life-sustaining treatments during the last three months of life. After adjusting for other covariates, those who underwent EOL discussions were less likely to receive life-sustaining treatments during the last three months of life compared to those who did not (Adjusted odds ratio [AOR]: 0.82; 95% confidence interval [CI]: 0.80–0.84). Considering the type of treatments, EOL discussions correlated with a lower likelihood of receiving cardiopulmonary resuscitation (AOR = 0.43, 95% CI: 0.41–0.45), endotracheal intubation (AOR = 0.87, 95%CI: 0.85–0.89), and defibrillation (AOR = 0.52, 95%CI: 0.48–0.57).

Conclusion

EOL discussions correlated with a lower utilization of life-sustaining treatments during the last three months of life among cancer patients. Our study supports the importance of providing these discussions to cancer patients to better align care with preferences during the EOL treatment.

Background

Cancer is the second leading cause of death worldwide, and was responsible for an estimated 10 million deaths in 2020 [1]. Patients often experience pain, dyspnea, and distress during the end-of-life (EOL) care. Aggressive EOL treatment has predicted lower quality of life [2, 3] and greater regret about treatment decisions [4].

Comprehensive EOL discussions with physicians could allow cancer patients to confront the limitations of medical treatments and consider their preferences regarding life-sustaining treatments in extremis. A meta-analysis review showed that these discussions predicted an increased use of hospice care and better quality of death [5]. However, cancer patients often ignore the provision of EOL discussions [6, 7] and initiate them late in the disease's progression [8].

Although EOL discussions offer patients the opportunity to define their expectations for life-sustaining treatments that they want to receive in extremis, studies to examine the impact of EOL discussions on the utilization of life-sustaining treatments near death were limited and had inconsistent findings. A US cohort study followed up 332 patients with advanced cancer and found that patients who participated in EOL discussions were less likely to receive ventilation (Adjusted odds ratio [AOR]: 0.26; 95% confidence interval [CI]: 0.08-0.83) and resuscitation (AOR 0.16, 95% CI 0.03-0.80) during the EOL treatment compared to those who did not [6]. In another observational study in the US involving 145 patients with advanced cancer, EOL discussions significantly correlated with a lower rate of receiving ventilation (AOR 0.03, 95% CI 0.002-0.3) but did not significantly associate with a lower rate of resuscitation (AOR 0.1, 95% CI 0.02-1.3) [2]. Previous studies on the association between EOL discussions and the use of life-sustaining treatment, however, have used small sample sizes (n=145) [2] and inadequately controlled for potential confounders such as dementia [2, 6].

EOL discussions serve to maximize patients' quality of life while considering their goals and expectations regarding EOL treatment. It is important to understand the impact of these discussions on the administration of life-sustaining treatments among terminally ill patients. We therefore conducted a nationwide population-based cohort study to determine the impact of EOL discussions on the utilization of life-sustaining treatments in extremis among Taiwanese cancer patients, from 2012-2018.

Methods

Promotion of end-of-life discussions in terminally ill patients in Taiwan

The Taiwan National Health Insurance Administration, since 2012, has initiated an EOL discussions program that encourages healthcare providers to provide these discussions to terminally ill patients [9]. During the discussions, healthcare providers discuss patients' goals and preferences concerning medical care and life-sustaining treatments towards the end of their lives [9]. Each EOL discussion with a patient awards the healthcare provider with the equivalent of US\$75 [9]. There should be a record of all discussion content in the patient's medical chart and each session must be at least an hour long [9].

Study population

This nationwide cohort study used the Taiwan National Health Insurance Research Database (NHIRD), which contains healthcare data from more than 99% of the population in Taiwan [10]. It is a large-scale database derived from the national health insurance system, which consists of registration files and

original claims data. The database de-identified and scrambled the patients' identification codes before releasing the data for research purposes [11].

This cohort study selected subjects aged 18 years or older who had received a cancer diagnosis and died between January 1, 2012 and December 31, 2018. We identified these patients from the Registry for Catastrophic Illness. In Taiwan, the Registry for Catastrophic Illness requires a peer review of pathohistological reports before a cancer diagnosis is reported [12]. This registry was also linked to Taiwan's death certificate database to confirm the demise of cancer patients [13]. The Institutional Review Board of TCH (no. TCHIRB-10709107-W) approved this study and we performed all methods in accordance with TCH IRB guidelines and regulations.

Outcome variable

The outcome was life-sustaining treatments during the last three months of life in cancer patients. Life-sustaining treatments included cardiopulmonary resuscitation, intubation, and defibrillation [14].

Main explanatory variable

The main explanatory variable was EOL discussions with physicians, which was determined by patients' medical records.

Controlling variables

The controlling variables included sociodemographic characteristics and comorbidities. Sociodemographic factors included age, sex, urbanization, and income level. Urbanization described whether subjects resided in urban, suburban, or rural areas [15]. We calculated the income level from the average monthly income of the insured person and grouped it into three categories: low ($\leq$ 19,200 New Taiwan Dollars [NTD]), intermediate (19,201 NTD to $<$ 40,000 NTD), and high ($\geq$ 40,000 NTD). We defined the comorbidities according to the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) code. Subjects' comorbidities include diabetes, chronic kidney disease, congestive heart failure, coronary heart disease, liver cirrhosis, chronic obstructive pulmonary disease, dementia, and cerebrovascular disease (Supplementary table 1). A person was considered to have a comorbidity only if the condition occurred in an inpatient setting or in three or more outpatient visits [16].

Statistical analysis

First, we analyzed the subjects' demographic data. We then analyzed categorical data using the Pearson χ^2 test where appropriate. We presented continuous data as mean $\pm$ standard deviation (SD), and conducted a two-sample t-test to compare outcomes between patients who underwent EOL discussions and those who did not.

We assessed the crude associations of EOL discussions and other covariates with the outcome (utilization of life-sustaining treatments during the last three months of life) by computing the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). We then performed a multivariate logistic regression to estimate the association between EOL discussions and the utilization of life-sustaining treatments after adjusting for potential confounders. A variable with $p < 0.05$ was defined as a significant factor associated with the utilization of life-sustaining treatments in the multivariate analysis. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) indicated the strength and direction of these associations.

We conducted subgroup and sensitivity analyses to examine the robustness of the main findings, after stratifying participants by age and sex. We performed all data management and analyses using the SAS® v9.4 statistical software package (SAS Institute, Cary, NC, USA).

Results

Participant selection

This cohort study involved the raw data of 383,128 deceased cancer patients from 1 January 2012 to 31 December 2018. After excluding those younger than 15 years ($n = 850$) and those with missing data ($n=1071$), 381,207 patients were eligible for the purposes of the study. The overall mean (SD) age was 70.5 (14.3) years; 65.6% of the subjects were male; and 14.1% of the subjects had EOL discussions with healthcare providers towards the end of their lives.

Characteristics of patients by end-of-life discussions

Table 1 shows the characteristics of cancer patients with and without EOL discussions before death. The patients who participated in EOL discussions tended to be younger and were more likely to be female. During the follow-up period, 74,034 patients utilized life-sustaining treatments during their last three months of life, including 9,048 (16.82%) patients who had EOL discussions and 64,986 (19.85%) who did not have EOL discussions.

Association of end-of-life discussions with utilization of life-sustaining treatments

Table 2 shows the univariate and multivariate analyses of factors associated with life-sustaining treatments during the last three months of life among the cancer patients. After adjusting for the sociodemographic factors and co-morbidities, those who underwent EOL discussions were less likely to receive life-sustaining treatments during the last three months of life, compared to those who did not (AOR=0.82, 95% CI: 0.80-0.84).

Association of end-of-life discussions with cardiopulmonary resuscitation, endotracheal intubation, and defibrillation

Table 3 shows the multivariate analyses for the association of EOL discussions with cardiopulmonary resuscitation, endotracheal intubation, and defibrillation in cancer patients. After adjusting for the sociodemographic factors and co-morbidities, patients who underwent EOL discussions were less likely to receive cardiopulmonary resuscitation during their last three months of life, compared to those who did not (AOR=0.43, 95% CI: 0.41-0.45). Moreover, those who participated in EOL discussions had a lower likelihood of receiving endotracheal intubation (AOR=0.87, 95% CI: 0.85-0.89) and defibrillation (AOR=0.52, 95% CI: 0.48-0.57) during the last three months of life, compared to those who did not.

Subgroup and sensitivity analysis for the association between end-of-life discussions and life-sustaining treatments

Table 4 shows the results of subgroup analyses of the association between EOL discussions and life-sustaining treatments after stratifying participants by age and sex. In all patient subgroups, the discussions significantly predicted a lower likelihood of receiving life-sustaining treatments towards the end of life.

Discussion

This nationwide cohort study found that 19.4% of cancer patients utilized life-sustaining treatments during the last three months of life. After adjusting for demographic data and comorbidities, cancer patients who underwent EOL discussions were less likely to receive life-sustaining treatments during EOL care. With regard to the treatment types, EOL discussions predicted a lower likelihood of receiving cardiopulmonary resuscitation, endotracheal intubation, and defibrillation towards the end of the patients' lives.

Our study revealed robust associations between EOL discussions and life-sustaining treatments after stratifying patients by age and sex. In all patient subgroups, the discussions significantly lowered the likelihood of receiving life-sustaining treatments near death.

This study found that 14.1% of cancer patients in Taiwan participated in EOL discussions, which was lower than 37.0% among cancer patients in the US [6]. These discussions provide patients the opportunity to define their goals and expectations regarding the medical care that they would like to receive in extremis [17]. Since EOL discussions with physicians comprehensively informed patients' wishes with respect to EOL care, our study suggests that it is imperative to provide such discussions for cancer patients nearing the end of their lives.

The present cohort study found that cancer patients who underwent EOL discussions had 18% lower rates of receiving life-sustaining treatments in the last three months of life, than those who did not.

Although EOL discussions offer patients the opportunity to define their preferences regarding life-sustaining treatments in extremis, the impact of EOL discussions on the utilization of life-sustaining treatments near death has not been extensively studied. A study in the US found that EOL discussions

correlated with lower rates of ventilation and resuscitation near death [6]. Another study in the US analyzed 145 cancer patients and found that patients who had undergone EOL discussions were less likely to receive ventilation in the last week of life, but were not less likely to receive resuscitation in the same timeframe [2]. Our cohort study followed up 381,207 cancer patients and found that EOL discussions associated with a lower utilization of life-sustaining treatments during the last three months of life. With regard to treatment types, cancer patients who had EOL discussions had a lower likelihood of receiving cardiopulmonary resuscitation, endotracheal intubation, and defibrillation during EOL care. Thus the findings of our study suggest that EOL discussions could reduce the utilization of life-sustaining treatments in cancer patients near death.

The EOL conversations with physicians improved the patients' understanding of the benefits of aggressive therapies during EOL care. This may account for the lower rate of receiving life-sustaining treatments at that stage. While cancer patients had EOL discussions with physicians, the benefit and harm of life-sustaining treatments during the EOL care would be discussed and emphasized. Through the EOL discussions with healthcare providers, cancer patients could consider and document their treatment preferences during EOL care. A prior study showed that EOL discussions significantly improved patients' understanding of their terminal illness and subsequently reduced the likelihood of receiving aggressive treatments during EOL care [18]. Since EOL discussions improved patient satisfaction and quality of care [19, 20], the findings of our study suggest that it is important to provide them to better align care with preferences during EOL treatment.

This nationwide cohort study has several strengths. First, this study is the largest cohort study to determine the impact of EOL discussions on the utilization of life-sustaining treatments during the last three months of life among cancer patients. The research design enhances the validity of our findings by including unbiased subject selection and strict cancer diagnostic criteria. Moreover, since the Taiwan National Health Insurance covers all medical care of cancer patients, this nationwide population-based study traced all cancer patients, thus minimizing referral bias. Furthermore, the study's large sample size sufficiently detected the real, albeit subtle, difference between cancer patients who had and those who had not received EOL discussions towards the end of their lives.

This cohort study has two limitations. First, there may be important factors (e.g., patients' religion) associated with the decision of receiving life-sustaining treatments, which the National Health Insurance Research Database did not record. Second, since all our enrollees were Taiwanese, the external validity of our findings may be a concern. Therefore, the generalizability of our results to other non-Asian ethnic groups requires further verification. However, our findings suggest new avenues for future research.

Conclusions

This nationwide, cohort study found that cancer patients who had EOL discussions were less likely to receive life-sustaining treatments during the last three months of life compared to those who did not have EOL discussions. With regard to treatment types, EOL discussions correlated with a lower likelihood of

receiving cardiopulmonary resuscitation, endotracheal intubation, and defibrillation during the last three months of life. Since EOL discussions improve patient quality of care, the findings of our study suggest that it is important to provide them to better align care with preferences during EOL treatment.

Declarations

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Conflicts of interest/Competing interests The authors declare that they have no conflict of interest.

Availability of data and material This nationwide cohort study used the Taiwan National Health Insurance Research Database (NHIRD). With approval from the National Health Research Institutes, the NHIRD was accessed at the Collaboration Center of Health Information Application, Department of Health, Executive Yuan, Taiwan.

Code availability N/A

Authors' contributions Shang-Yih Chan, Yun-Ju Lai, Yu-Yen Chen, Shuo-Ju Chiang, Yi-Fan Tsai, Li-Fei Hsu, Pei-Hung Chuang, Chu-Chieh Chen, and Yung-Feng Yen substantially contributed to the conception and design of the study, data analysis, data interpretation, and the drafting of the manuscript. Shang-Yih Chan, Yun-Ju Lai, Yu-Yen Chen, Yi-Fan Tsai, Li-Fei Hsu, Pei-Hung Chuang, Chu-Chieh Chen, and Yung-Feng Yen substantially contributed to data acquisition and interpretation of the results. Shang-Yih Chan, Yun-Ju Lai, Yu-Yen Chen, Shuo-Ju Chiang, Yi-Fan Tsai, Li-Fei Hsu, Pei-Hung Chuang, Chu-Chieh Chen, and Yung-Feng Yen all approved the final version of the manuscript.

Ethics approval This study was approved by the Institutional Review Board of TCH (no. TCHIRB-10709107-W) and all methods were performed in accordance with TCH IRB guidelines and regulations.

Consent to participate N/A

Consent for publication N/A

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Tables

Table 1
Characteristics of deceased cancer patients by end-of-life discussions

Characteristics	No. (%) of subjects*			P value
	Total, N = 381207	Patients with EOL discussions, n = 53783	Patients without EOL discussions, n = 327424	
Demographics				
Age, yrs				
Mean ± SD	70.46 ± 14.26	69.19 ± 14.21	70.66 ± 14.26	< .001
18–64	131034 (34.37)	20302 (37.75)	110,732 (33.82)	< .001
≥65	250173 (65.63)	33,481 (62.25)	216,692 (66.18)	
Sex				
Female	147147 (38.60)	21,226 (39.47)	125,921 (38.46)	< .001
Male	234060 (61.40)	32,557 (60.53)	201,503 (61.54)	
Income level				
Low	64059 (16.80)	8,745 (16.26)	55,314 (16.89)	< .001
Intermediate	195861 (51.38)	26,823 (49.87)	169,038 (51.63)	
High	121287 (31.82)	18,215 (33.87)	103,072 (31.48)	
Urbanization				
Rural	44575 (11.69)	5,358 (9.96)	39,217 (11.98)	< .001
Suburban	232349 (60.95)	32,814 (61.01)	199,535 (60.94)	
Urban	104283 (27.36)	15,611 (29.03)	88,672 (27.08)	
Comorbidity				
Diabetes	135886 (35.65)	19,087 (35.49)	116,799 (35.67)	0.411

Characteristics	No. (%) of subjects*			P value
	Total, N = 381207	Patients with EOL discussions, n = 53783	Patients without EOL discussions, n = 327424	
Chronic kidney disease	87396 (22.93)	11,282 (20.98)	76,114 (23.25)	< .001
Congestive heart failure	59996 (15.74)	7,786 (14.48)	52,210 (15.95)	< .001
Coronary heart disease	124070 (32.55)	16,296 (30.30)	107,774 (32.92)	< .001
Liver cirrhosis	57255 (15.02)	7,697 (14.31)	49,558 (15.14)	< .001
COPD	118345 (31.04)	15,677 (29.15)	102,668 (31.36)	< .001
Dementia	37402 (9.81)	4,790 (8.91)	32,612 (9.96)	< .001
Cerebrovascular disease	102614 (26.92)	13,501 (25.10)	89,113 (27.22)	< .001
Outcome				
Life-sustaining treatments during the last 3 months of life	74034 (19.42)	9048 (16.82)	64986 (19.85)	< .001
Endotracheal intubation	66,861	8,483 (15.77)	58,378 (17.83)	< .001
Cardiopulmonary resuscitation	32,739	2,269 (4.22)	30,470 (9.31)	< .001
Defibrillation	6,493	514 (0.96)	5,979 (1.83)	< .001
EOL end-of-life, SD standard deviation, COPD chronic obstructive pulmonary disease, *Unless stated otherwise.				

Table 2

Univariate and multivariate analysis of factors associated with utilization of life-sustaining treatments during the last 3 months of life among deceased cancer patients

Variables	Number of patients	Life-sustaining treatments ^a	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
EOL discussions				
No	327,424	64986 (19.85)	1	1
Yes	53,783	9048 (16.82)	0.82 (0.80–0.84) ^{***}	0.82 (0.80–0.84) ^{***}
Demographics				
Age, yrs				
18–64	131,034	25318 (19.32)	1	1
≥65	250,173	48716 (19.47)	1.01 (0.99–1.03)	0.85 (0.83–0.87) ^{***}
Sex				
Female	147,147	24875 (16.90)	1	1
Male	234,060	49159 (21.00)	1.31 (1.29–1.33) ^{***}	1.31 (1.29–1.34) ^{***}
Income level				
Low	64,059	13046 (20.37)	1	1
Intermediate	195,861	37507 (19.15)	0.93 (0.91–0.95) ^{***}	0.97 (0.95–0.99) ^{**}
High	121,287	23481 (19.36)	0.94 (0.92–0.96) ^{***}	0.99 (0.97–1.01)
Urbanization				
Rural	44575	8754 (19.64)	1	1
Suburban	232349	45238 (19.47)	0.99 (0.96–1.02)	0.99 (0.96–1.01)
Urban	104283	20042 (19.22)	0.97 (0.95-1.00)	0.98 (0.95–1.01)
Comorbidity				

Variables	Number of patients	Life-sustaining treatments ^a	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
Diabetes				
No	245,321	45400 (18.51)	1	1
Yes	135,886	28634 (21.07)	1.18 (1.16–1.20)***	1.11 (1.09–1.13)***
Chronic kidney disease				
No	293,811	54038 (18.39)	1	1
Yes	87,396	19996 (22.88)	1.32 (1.29–1.34)***	1.21 (1.19–1.24)***
Congestive heart failure				
No	321,211	59746 (18.60)	1	1
Yes	59,996	14288 (23.81)	1.37 (1.34–1.40)***	1.24 (1.21–1.27)***
Coronary heart disease				
No	257,137	46786 (18.19)	1	1
Yes	124,070	27248 (21.96)	1.27 (1.24–1.29)***	1.14 (1.12–1.16)***
Liver cirrhosis				
No	323,952	63979 (19.75)	1	1
Yes	57,255	10055 (17.56)	0.87 (0.85–0.89)***	0.84 (0.82–0.86)***
COPD				
No	262,862	49016 (18.65)	1	1
Yes	118,345	25018 (21.14)	1.17 (1.15–1.19)***	1.05 (1.04–1.07)***
Dementia				
No	343,805	66583 (19.37)	1	1

Variables	Number of patients	Life-sustaining treatments ^a	Univariate	Multivariate analysis
		n (%)	OR (95%CI)	AOR (95%CI)
Yes	37,402	7451 (19.92)	1.04 (1.01–1.06) ^{**}	0.95 (0.92–0.97) ^{***}
Cerebrovascular disease				
No	278,593	51892 (18.63)	1	1
Yes	102,614	22142 (21.58)	1.20 (1.18–1.22) ^{***}	1.11 (1.09–1.14) ^{***}
^{**} <.01, ^{***} <.001				
AOR adjusted odds ratio, CI confident interval, EOL end-of-life, COPD chronic obstructive pulmonary disease.				
^a During the last 3 months of life.				

Table 3

Multivariate analysis for the association of end-of-life discussions with cardiopulmonary resuscitation, endotracheal intubation, and defibrillation in deceased cancer patients

Variables	Cardiopulmonary resuscitation ^a	Intubation ^a	Defibrillation ^a
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
EOL discussions	0.43 (0.41–0.45) ^{***}	0.87 (0.85–0.89) ^{***}	0.52 (0.48–0.57) ^{***}
Age, yrs			
18–64	1	1	1
≥65	0.90 (0.87–0.92) ^{***}	0.86 (0.84–0.87) ^{***}	0.74 (0.70–0.79) ^{***}
Male gender	1.24 (1.21–1.27) ^{***}	1.31 (1.28–1.33) ^{***}	1.31 (1.24–1.38) ^{***}
Income level			
Low	1	1	1
Intermediate	0.92 (0.90–0.95) ^{***}	0.98 (0.96–1.01)	1.10 (1.02–1.18) [*]
High	0.91 (0.88–0.94) ^{***}	1.00 (0.98–1.03)	1.17 (1.08–1.26) ^{***}
Urbanization			
Rural	1	1	1
Suburban	1.00 (0.97–1.04)	0.98 (0.96–1.01)	1.03 (0.95–1.11)
Urban	1.02 (0.97–1.06)	0.96 (0.93–0.99) ^{**}	1.10 (1.00–1.20) [*]
Comorbidity			
Diabetes	1.14 (1.12–1.17) ^{***}	1.11 (1.09–1.13) ^{***}	1.17 (1.11–1.24) ^{***}
Chronic kidney disease	1.18 (1.15–1.22) ^{***}	1.21 (1.19–1.24) ^{***}	1.31 (1.24–1.38) ^{***}
Congestive heart failure	1.35 (1.31–1.39) ^{***}	1.22 (1.19–1.25) ^{***}	1.97 (1.85–2.09) ^{***}

Variables	Cardiopulmonary resuscitation ^a	Intubation ^a	Defibrillation ^a
	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Coronary heart disease	1.22 (1.19–1.25) ^{***}	1.14 (1.12–1.16) ^{***}	1.60 (1.51–1.69) ^{***}
Liver cirrhosis	0.68 (0.66–0.71) ^{***}	0.86 (0.84–0.89) ^{***}	0.71 (0.65–0.76) ^{***}
COPD	1.03 (1.01–1.06) [*]	1.04 (1.02–1.06) ^{***}	0.87 (0.82–0.92) ^{***}
Dementia	1.05 (1.01–1.09) [*]	0.92 (0.89–0.95) ^{***}	0.79 (0.72–0.86) ^{***}
Cerebrovascular disease	1.03 (1.00–1.06)	1.12 (1.10–1.14) ^{***}	0.97 (0.91–1.02)
* <.05, *** <.001			
AOR adjusted odds ratio, CI confident interval, EOL end-of-life, COPD chronic obstructive pulmonary disease.			
^a During last 3 months of life.			

Table 4

Sensitivity analysis for the associations between end-of-life discussions and life-sustaining treatment after adjusting for patient characteristics

Study subgroups	Life-sustaining treatments	Cardiopulmonary resuscitation	Endotracheal intubation	Defibrillation
	AOR (95% CI)			
All patients (n = 381207)	0.82 (0.80–0.84) ^{***}	0.43 (0.41–0.45) ^{***}	0.87 (0.85–0.89) ^{***}	0.52 (0.48–0.57) ^{***}
Aged 18–64 (n = 131034)	0.83 (0.80–0.87) ^{***}	0.46 (0.42–0.49) ^{***}	0.88 (0.85–0.92) ^{***}	0.57 (0.49–0.65) ^{***}
Aged ≥ 65 (n = 250173)	0.82 (0.79–0.84) ^{***}	0.42 (0.40–0.44) ^{***}	0.86 (0.84–0.89) ^{***}	0.50 (0.45–0.56) ^{***}
Female patients (n = 147147)	0.82 (0.79–0.85) ^{***}	0.43 (0.40–0.47) ^{***}	0.86 (0.83–0.90) ^{***}	0.51 (0.44–0.60) ^{***}
Male patients (n = 234060)	0.83 (0.80–0.85) ^{***}	0.43 (0.41–0.46) ^{***}	0.87 (0.85–0.90) ^{***}	0.53 (0.48–0.60) ^{***}
^{***} <.001				
AOR adjusted odds ratio, CI confident interval.				

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