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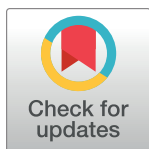
Timing is everything: Early do-not-resuscitate orders in the intensive care unit and patient outcomes

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Abstract

Background

The use of Do-Not-Resuscitate (DNR) orders has increased but many are placed late in the dying process. This study is to determine the association between the timing of DNR order placement in the intensive care unit (ICU) and nurses' perceptions of patients' distress and quality of death.

Methods

200 ICU patients and the nurses (n = 83) who took care of them during their last week of life were enrolled from the medical ICU and cardiac care unit of New York Presbyterian Hospital/Weill Cornell Medicine in Manhattan and the surgical ICU at the Brigham and Women's Hospital in Boston. Nurses were interviewed about their perceptions of the patients' quality of death using validated measures. Patients were divided into 3 groups—no DNR, early DNR, late DNR placement during the patient's final ICU stay. Logistic regression analyses modeled perceived patient quality of life as a function of timing of DNR order placement. Patient's comorbidities, length of ICU stay, and procedures were also included in the model.

Results

59 patients (29.5%) had a DNR placed within 48 hours of ICU admission (early DNR), 110 (55%) placed after 48 hours of ICU admission (late DNR), and 31 (15.5%) had no DNR order placed. Compared to patients without DNR orders, those with an early but not late DNR order placement had significantly fewer non-beneficial procedures and lower odds of being rated by nurses as not being at peace (Adjusted Odds Ratio namely AOR = 0.30; [CI = 0.09–0.94]), and experiencing worst possible death (AOR = 0.31; [CI = 0.1–0.94]) before controlling for procedures; and consistent significance in severe suffering (AOR = 0.34; [CI

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= 0.12–0.96]), and experiencing a severe loss of dignity (AOR = 0.33; [CI = 0.12–0.94]), controlling for non-beneficial procedures.

Conclusions

Placement of DNR orders within the first 48 hours of the terminal ICU admission was associated with fewer non-beneficial procedures and less perceived suffering and loss of dignity, lower odds of being not at peace and of having the worst possible death.

Introduction

Cardiopulmonary Resuscitation (CPR) was introduced to clinical practice in the 1960's [1] and became a default treatment for patients with cardiac arrest regardless of their underlying injury or disease.[2] Since that time, however, it has become clear that CPR does not necessarily benefit patients who are terminally ill.[3–5] Do-Not-Resuscitate (DNR) orders are an alternative for patients at the end of life,[3] to prevent receipt of nonbeneficial procedures (e.g. CPR) and unnecessary suffering when patients are imminently dying.[6, 7]

In recent decades, the number of Americans who spend part of their last month of life in the Intensive Care Unit (ICU) has increased to near 30%. Over this same period, the use of DNR orders has increased, [8–11] however most DNR orders are placed very close to the time of death, with a high percentage of DNR orders placed within 24 hours of death.[11–13]

Little is known about the relationship between the timing of DNR orders and patients' quality of death. Results from our recently published report on nurse perception of suffering at the end of life in the ICU did not demonstrate an association between DNR status and quality of death, but did not distinguish early from late DNR.[14] Few studies have examined the timing of DNR orders and its association with mortality, length of stay, interventions, and cost. [15–18] To our knowledge, no previous studies have reported associations between DNR timing and patient-centered outcomes, such as physical or emotional distress, peacefulness, suffering or loss of dignity.

In the present study, we hypothesized that compared to late DNR (orders placed after the first 48 hours of ICU admission), early DNR (orders placed prior to or within the first 48 hours of ICU admission) would be associated with higher quality of death in the ICU; including less nurse-perceived physical distress, psychological distress, suffering and loss of dignity.

Materials and methods

Weill Cornell Medicine (WCM) Institutional Review Board (IRB) approved this clinical observational trial (IRB 1504016102). IRB approval was obtained from all participating study sites. A full waiver for consent from deceased patients was approved by IRB at New York Presbyterian Hospital/Weill Cornell Medicine (NYP/WCM) and Brigham and Women's Hospital (BWH). Written informed consent was obtained from all nurses participated in the study. All study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was discussed regularly between the study principal investigator and co-investigators and reviewed by IRB at least once a year to ensure the protocol was rigorously followed.

Study design

From September 2015 to March 2017, data were collected from nurses to assess the quality of life of 200 patients who died in the Medical ICU (MICU) or Cardiac Care Unit (CCU) of NYP/WCM in Manhattan or the Surgical ICU (SICU) at BWH in Boston. Nurses' evaluations of the quality of life in the patient's last week were assessed. Data from the patients' medical charts were abstracted to confirm clinical information about patients, medical care received and timing of DNR orders.

Each week, trained study staff screened consecutive patients who died in the MICU and CCU at New York Presbyterian Hospital/Weill Cornell Medicine ($n = 358$), or in the SICU at Brigham and Women's Hospital ($n = 64$) to identify a nurse who cared for the decedents for at least one 12-hour shift in their last week of life. After obtaining their informed consent, nurses were interviewed individually and in person. Nurse participation occurring outside of work hours was compensated with a \$20 gift card per person. Nurses were selected to be the primary assessors of patients' experiences just prior to death because several studies have demonstrated that nurses provide accurate assessments of patients' experience at the end of life, and can accurately predict in-hospital outcomes, particularly when compared to physicians and family members [19–23].

Data collection

Ninety-eight percent of the nurses approached (100/102) agreed to participate in the study, and 83% (83/100) were selected for data analysis based on the number of shifts, the time between their shifts and patients' death, and presence at patients' death. For some patients, multiple nurses who cared for them were interviewed. And in these cases, we selected the nurses with the most shifts caring for the patient in the last week of life. A variable that captured the time between nurses' last shift and patients' death was used to determine the nurses for analysis if more than one nurse had the same number of shifts; In that case, we selected the nurse whose shift was closest to the time of the patient's death. Nurses who were present at the patient's death were prioritized and selected in this way. Each patient was cared by the interviewed nurse for 2.41 shifts (standard deviation = 1.04), 65 patients had interviewed nurses who were present at their death, and 37 patients had unknown information on if the interviewed nurses were present at the patient's death).

The most common reason that otherwise eligible patients were excluded was due to nurse scheduling conflicts; 70 patients were excluded because they were in the ICU for less than 24 hours and did not have a nurse who took care of them for an entire shift. Trained staff conducted structured clinical interviews with the nurse within three weeks of the patient's death.

Patient demographics, diagnoses, care received, and DNR status were abstracted from medical charts. Orders, admission notes, resuscitation records and death notes were reviewed and checked by trained staff to obtain accurate time and date of ICU admission, DNR placement, and death. Use of life-sustaining therapies, including mechanical ventilation, renal replacement therapy, feeding tubes, and vasopressors was also documented from the medical charts.

Measures

All of the measures below have been validated in prior published work.[14]

DNR order status. The information about DNR orders was collected via inpatient electronic medical record systems. Date and time of each DNR was documented if multiple orders were placed. The person who agreed to sign the DNR and his/her relationship to patient was documented in medical notes. Patients who had a DNR order placed prior to or during the first 48 hours of ICU admission, as documented in the patient's medical chart, were coded as

'Early DNR'. Patients who had a DNR order written after 48 hours of ICU admission were coded as 'Late DNR'. Those who died without a DNR order in place were coded as 'No DNR'.

Medical care in the last week of life. Use of invasive therapies including chemotherapy, vasopressors, dialysis, mechanical ventilation, feeding tubes, cardiac resuscitation, and surgery were abstracted from the medical chart together with other information such as comorbidities, date/time and cause of death. Data were entered into safe, and secure online database. The decision to withdraw life- support was also documented.

Patient symptoms. Nurses evaluated common ICU patient symptoms that may have contributed to suffering. These symptoms included trouble breathing, edema, physical pain, painful broken skin, thirst, nausea or vomiting, fecal incontinence, constipation or diarrhea, urinary incontinence, loss of control of limbs, fever or chills, fatigue and difficulty sleeping.

Perceptions of patient quality of life and suffering. Measures of the patient experience in the last week of life were developed based on prior literature and discussions with ICU physicians, nurses, and end-of-life specialists and validated in a prior study.[14]

During structured interviews, nurses were asked to rate items on a scale from 1 to 10, where 1 was defined as best possible and 10 was defined as worst possible and the items included the decedents' physical and psychological distress, appearing at peace, having the worst possible death, suffering and loss of dignity. The assessment was based on the previously validated questions on patient quality of life in the last week of life.[19] Scores of 8 or higher on this scale were distinguished from lower scores to represent patients with severe symptoms. The suffering and loss of dignity measures were associated with previously validated measures of psychological distress, physical distress, and overall quality of death, and peacefulness at the end of life, [24–27] with results demonstrated highly significant associations (all $p < 0.001$).

Data analysis

Means and percentages were used to summarize patient characteristics for the total analytic sample and by DNR status. Analysis of variance (ANOVA) or its non-parametric counterpart Kruskal-Wallis test was employed to compare patient characteristics represented by continuous variables, depending on whether the assumption of normal distribution was satisfied. Chi-square tests were used for categorical variables respectively, to test marginal associations between patient characteristics and DNR status. Items with significantly small p-values (<0.05) indicating imbalanced distribution among 3 DNR groups: early, late and no DNR) were considered as possible confounders including age, gender, length of ICU stay and Charlson Comorbidity Index (CCI) and these were adjusted for in the following analyses. Three sets of logistic regression models were then estimated: 1) invasive procedures were regressed on patients' DNR status adjusting for identified possible confounders; 2) nurse-evaluated patient quality of death was regressed on DNR status adjusting for age, gender, race, and length of ICU stay; and 3) nurse-evaluated patient quality of death outcomes were regressed on DNR status, adjusting for same set of confounders, or adjusting for these same confounders and a sum of significant non-beneficial procedures detected above. A p-value of 0.05 was used in all analyses as the threshold for determining statistical significance. R version 3.5.1 was used to perform all statistical analyses.

Results

Of the 200 assessed decedent patients, 30 (15%) died in the SICU, 25 (12.5%) in the CCU, and 145 (72.5%) in the MICU. 59 patients (29.5%) had a DNR placed within 48 hours of ICU admission (early DNR), 110 (55%) had DNR orders placed after 48 hours of ICU admission (late DNR), and 31 (15.5%) had no DNR order in place.

Most patients were 65 years or older at the time of ICU admission (Median $M = 66.9$ years; $SD = 15.2$), male (61.0%), and white (63.5%). Most patients received life-sustaining medical interventions during their ICU stay, the most common were vasopressors (86.5%) and mechanical ventilation (81.5%). DNR orders were placed for 34 patients (17%) after having a cardiac arrest and receiving CPR and 44 patients (22%) received CPR within 48 hours of death.

Patients of different DNR groups varied by age ($p < 0.001$), Charlson Comorbidity Index (CCI) scores ($p = 0.025$), gender ($p = 0.031$) and length of ICU stay ($p < 0.001$). The mean age of early DNR patients ($M = 73.3$) was higher than that of late ($M = 66.1$) or no DNR ($M = 57.5$) patients, and their mean CCI score ($M = 5.76$) greater than late ($M = 5.65$) or no DNR ($M = 4.35$) patients, suggesting that older patients, and those with more comorbidities tend to have DNR orders placed early. Although when comparing the difference in decision makers by early, late and no DNR order groups, the p value did not achieve a level of statistical significance $p = (0.053)$, there was a trend suggesting differences in timing of DNR placement by decision-maker. Specifically examining the relationship between decision-maker and each time period we found that DNR orders were more likely to be placed early when decided by patients themselves (Odds Ratio or OR = 2.9, $p = 0.039$) and were less likely if the spouse made the decision ($p < 0.01$). (Table 1)

After adjusting for possible confounders, patients with an early DNR order in place, compared to those with no DNR, were significantly less likely to receive certain medical interventions during their ICU stay, including dialysis (Adjusted Odds Ratio namely AOR = 0.22; [CI = 0.07–0.69]); mechanical ventilation (AOR = 0.16; [CI = 0.03–0.8]); feeding tube (AOR = 0.33; [CI = 0.11–0.96]); cardiac resuscitation (AOR = 0.05; [CI = 0.01–0.2]). No differences were detected between those with a late DNR or no DNR except for cardiac resuscitation (AOR = 0.04; [CI = 0.01–0.12]) and withdraw life support between (AOR = 3.98; [CI = 1.09–14.57]). (Table 2)

Adjusted analyses revealed further that patients with early DNR order placement had lower odds than those with no DNR orders of ratings by nurses indicating poor end-of-life outcomes, including not being at peace (AOR = 0.30; [CI = 0.09–0.94]), experiencing worst possible death (AOR = 0.31; [CI = 0.1–0.94]), suffering (AOR = 0.38; [CI = 0.14–0.99]), and experiencing a loss of dignity (AOR = 0.26; [CI = 0.09–0.7]). However, no difference was detected for the above terms when comparing late DNR patient group to no DNR group. Adjusted odds ratio comparing early vs no DNR group became insignificant for not being at peace (AOR = 0.41 [CI = 0.12–1.38]) and worst possible death (AOR = 0.32; [CI = 0.1–1.02]) when controlling for number of significant invasive procedures, suggesting these procedures accounted for the association between early DNR order placement and those outcomes. (Tables 3–5).

Discussion

Our results suggest that early DNR order placement (within 48 hours of ICU admission) for patients who die in the ICU is associated with fewer life-sustaining interventions and less nurse-perceived suffering and loss of dignity. Early DNR was also associated with decreased odds of being perceived by nurses as not at peace or having the worst possible death before adjusting for procedures such as dialysis, mechanical ventilation, feeding tube, cardiac resuscitation and withdrawal of life support.

Previous studies have examined the impact of early DNR in ICU patients on cost, procedures and mortality, but this is the first study, to our knowledge, to examine the relationship of DNR timing on patient distress, peacefulness and dignity. Consistent with the published

Table 1. Patient characteristics and their associations with patients' DNR order status (N = 200).

Variable	DNR Order Status									ANOVA/CHISQ
	Full Sample		Early DNR		Late DNR		No DNR		p	
	N = 200		N = 59 (29.5%)		N = 110 (55.0%)		N = 31 (15.5%)			
	mean	SD	mean	SD	mean	SD	mean	SD		
Age (years)	66.9	15.2	73.3	13	66.1	14.2	57.5	17.1	<0.001	
Charlson Comorbidity Index	5.48	2.54	5.76	2.15	5.65	2.59	4.35	2.81	0.025	
Variable	n	%	n	%	n	%	n	%	p	
Sex									0.031	
	Male	122	61.0%	28	47.5%	75	68.2%	19	61.3%	
	Female	78	39.0%	31	52.5%	35	31.8%	12	38.7%	
Race									0.052	
	White	127	63.5%	43	72.9%	69	62.7%	15	48.4%	
	Non-White	68	34.0%	15	25.4%	37	33.6%	16	51.6%	
DNR by									0.053	
	Spouse	67	39.6%	17	28.8%	50	45.5%	--	--	
	Family	67	39.6%	24	40.7%	43	39.1%	--	--	
	Non-Family	16	9.5%	7	11.9%	9	8.2%	--	--	
	Patient	19	11.2%	11	18.6%	8	7.3%	--	--	
Diagnosis									0.175	
	Respiratory Failure	63	31.5%	16	27.1%	36	32.7%	11	35.5%	
	Cardiac arrest	23	11.5%	9	15.3%	8	7.3%	6	19.4%	
	Sepsis/Septic Shock	26	13.0%	9	15.3%	14	12.7%	3	9.7%	
	Hemorrhage	21	10.5%	8	13.6%	8	7.3%	5	16.1%	
	Other	67	33.5%	17	28.8%	44	40.0%	6	19.4%	
Variable	M	IQR	M	IQR	M	IQR	M	IQR	p	
Days in ICU	7	8.25	3	3	9	10	5	7	<0.001*	

Notes: M = Median; IQR = Inter Quantile Range; SD = Standard Deviation

*p-value of Kruskal-Wallis test.

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Table 2. Patient care in the last week of life and its associations with patients' DNR order status (N = 200).

Procedure	DNR Order Status													
	Full Sample		Early DNR		Late DNR		No DNR		Early vs No			Late vs No		
	N = 200		N = 59		N = 110		N = 31		AOR ¹	CI	p	AOR ¹	CI	p
Chemotherapy	20	10.0%	3	5.1%	13	11.8%	4	12.9%	0.60	(0.11,3.33)	0.56	1.30	(0.36,4.73)	0.69
Vasopressors	173	86.5%	50	84.7%	94	85.5%	29	93.5%	0.66	(0.12,3.56)	0.63	0.58	(0.12,2.76)	0.49
Dialysis	67	33.5%	7	11.9%	47	42.7%	13	41.9%	0.22	(0.07,0.69)	0.01	1.12	(0.48,2.61)	0.79
Mechanical Ventilation	163	81.5%	39	66.1%	95	86.4%	29	93.5%	0.16	(0.03,0.8)	0.03	0.53	(0.11,2.52)	0.42
Feeding Tube	129	64.5%	28	47.5%	77	70.0%	24	77.4%	0.33	(0.11,0.96)	0.04	0.64	(0.24,1.74)	0.38
Cardiac Resuscitation	65	32.5%	16	27.1%	22	20.0%	27	87.1%	0.05	(0.01,0.2)	<0.01	0.04	(0.01,0.12)	<0.01
Surgery	27	13.5%	5	8.5%	17	15.5%	5	16.1%	0.51	(0.12,2.14)	0.36	0.96	(0.31,2.97)	0.94
Withdraw Life Support	52	26.0%	18	30.5%	31	28.2%	3	9.7%	3.18	(0.81,12.58)	0.10	3.98	(1.09,14.57)	0.04

Notes: AOR = Adjusted Odds Ratio; Associations of DNR status with patient symptoms are adjusted for age, gender, Charlson Comorbidity Index, and length of ICU stay.

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Table 3. Patient quality of life, suffering and their associations with patients' DNR order status (adjusted for different variables).

Quality of Death	DNR Order Status													
	Full Sample		Early DNR		Late DNR		No DNR		Early vs No			Late vs No		
	N (n)	%	N (n)	%	N (n)	%	N (n)	%	OR	CI	p	OR	CI	p
Physical Distress	183(53)	28.96%	57(22)	38.60%	98(26)	26.53%	28(5)	17.86%	2.89	(0.96,8.72)	0.060	1.66	(0.57,4.82)	0.351
Psychological Distress	137(35)	25.55%	41(12)	29.27%	78(17)	21.79%	18(6)	33.33%	0.83	(0.25,2.72)	0.755	0.56	(0.18,1.7)	0.305
Not at Peace	173(45)	26.01%	48(8)	16.67%	99(26)	26.26%	26(11)	42.31%	0.27	(0.09,0.81)	0.019	0.49	(0.2,1.19)	0.115
Worst Possible Death	190(67)	35.26%	56(24)	42.86%	104(37)	35.58%	30(6)	20.00%	0.33	(0.12,0.94)	0.038	0.45	(0.17,1.21)	0.113
Suffering	199(91)	45.73%	58(21)	36.21%	110(51)	46.36%	31(19)	61.29%	0.36	(0.15,0.88)	0.025	0.55	(0.24,1.23)	0.145
Loss of Dignity	194(81)	41.75%	55(15)	27.27%	108(48)	44.44%	31(18)	58.06%	0.27	(0.11,0.69)	0.006	0.58	(0.26,1.3)	0.183

Notes: OR = Odds Ratio; Bivariate associations of DNR status with patient symptoms.

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literature on the subject, [11–13] most patients in this cohort had a late DNR. As others have published, older patients, those with more comorbidities, and those who were white were more likely to have an early DNR [4, 28–30] Older patients and those with comorbidities may have more opportunity for discussion with their doctors and families about advanced directives and may be more likely to have accepted their own mortality.[31, 32] The racial disparity may be, in part, due to distrust of the health care system among patients who are members of racial or ethnic minority groups [33–35] who may perceive DNR orders as denying patients life-saving medical care.

These results highlight the difficulty family surrogates have in making decisions for their loved ones at the end of life while patients themselves are more likely to decide on early DNR. Several studies have shown the psychological stress placed on loved ones making decisions in the ICU, and these stresses persist after the loved one's death. Having conversations about DNR before or early in the ICU stay, when patients are more likely to have the capacity to make their own decisions not only promotes patient autonomy but also a higher probability of receipt of care concordant with their wishes. It may also save the family the additional stress of making these difficult decisions.[36, 37]

Invasive procedures at the end of life have been associated with poor quality of death.[38, 39] Patients who complete advance directives, including DNR orders, are less likely to receive nonbeneficial aggressive care at the end of life[40] and more likely to receive care consistent with their preferences.[41] Although the DNR order itself does not directly impact care until the moment of cardiac arrest, we found that decedents with early DNR received fewer invasive

Table 4. Patient quality of life, suffering and their associations with patients' DNR order status (adjusted for different variables).

Quality of Death	DNR Order Status													
	Full Sample		Early DNR		Late DNR		No DNR		Early vs No			Late vs No		
	N (n)	%	N (n)	%	N (n)	%	N (n)	%	AOR	CI	p	AOR	CI	p
Physical Distress	183(53)	28.96%	57(22)	38.60%	98(26)	26.53%	28(5)	17.86%	2.65	(0.82,8.51)	0.103	1.61	(0.55,4.74)	0.386
Psychological Distress	137(35)	25.55%	41(12)	29.27%	78(17)	21.79%	18(6)	33.33%	0.79	(0.22,2.89)	0.727	0.51	(0.16,1.62)	0.255
Not at Peace	173(45)	26.01%	48(8)	16.67%	99(26)	26.26%	26(11)	42.31%	0.30	(0.09,0.94)	0.038	0.47	(0.19,1.2)	0.115
Worst Possible Death	190(67)	35.26%	56(24)	42.86%	104(37)	35.58%	30(6)	20.00%	0.31	(0.1,0.94)	0.039	0.42	(0.15,1.14)	0.090
Suffering	199(91)	45.73%	58(21)	36.21%	110(51)	46.36%	31(19)	61.29%	0.38	(0.14,0.99)	0.048	0.55	(0.24,1.28)	0.165
Loss of Dignity	194(81)	41.75%	55(15)	27.27%	108(48)	44.44%	31(18)	58.06%	0.26	(0.09,0.7)	0.008	0.59	(0.26,1.35)	0.212

Notes: AOR = Adjusted Odds Ratio; Associations of DNR status with patient symptoms are adjusted for age, gender, CCI, length of ICU stay.

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Table 5. Patient quality of life, suffering and their associations with patients' DNR order status (adjusted for different variables).

Quality of death outcomes	Full Sample		DNR Order Status						Early vs No			Late vs No		
	N (n)	%	Early DNR		Late DNR		No DNR		AOR	CI	p	AOR	CI	p
			N (n)	%	N (n)	%	N (n)	%						
Physical Distress	183(53)	28.96%	57(22)	38.60%	98(26)	26.53%	28(5)	17.86%	3.26	(0.96,11.1)	0.059	1.78	(0.6,5.32)	0.301
Psychological Distress	137(35)	25.55%	41(12)	29.27%	78(17)	21.79%	18(6)	33.33%	1.03	(0.26,4.02)	0.964	0.57	(0.18,1.83)	0.345
Not at Peace	173(45)	26.01%	48(8)	16.67%	99(26)	26.26%	26(11)	42.31%	0.41	(0.12,1.38)	0.150	0.56	(0.22,1.45)	0.234
Worst Possible Death	190(67)	35.26%	56(24)	42.86%	104(37)	35.58%	30(6)	20.00%	0.32	(0.1,1.02)	0.054	0.42	(0.15,1.17)	0.097
Suffering	199(91)	45.73%	58(21)	36.21%	110(51)	46.36%	31(19)	61.29%	0.34	(0.12,0.96)	0.041	0.53	(0.23,4.35)	0.142
Loss of Dignity	194(81)	41.75%	55(15)	27.27%	108(48)	44.44%	31(18)	58.06%	0.33	(0.12,0.94)	0.038	0.66	(0.29,1.54)	0.340

Notes: AOR = Adjusted Odds Ratio; Associations of DNR status with patient symptoms are adjusted for age, gender, CCI, length of ICU stay, and number of procedures taken among dialysis, mechanical ventilation, feeding tube, cardiac resuscitation, and withdraw life support.

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interventions in the last week of life, including dialysis, mechanical ventilation, feeding tubes, and CPR compared to those with late DNR and no DNR. These associations may be explained by early conversations about goals of care including invasive procedures, such as dialysis, in addition to DNR orders. Along similar lines, early DNR orders may have been placed along with orders for comfort-focused care, which generally does not include invasive procedures. Understanding the nature and breadth of the conversations which led to the DNR orders is beyond the scope of this study.

All interviewed nurses were blinded on the topic of possible analysis between the timing of DNR and quality of death, and compared to patients with no DNR order, those patients with early DNR orders had significantly lower odds of being not at peace, having the worst possible death, suffering or loss of dignity even after adjusting for confounders including age, gender, CCI and length of ICU stay. Further adjustment for invasive procedures explained away the association between early DNR and peacefulness and having the worst possible death. This suggests that invasive procedures may be the mechanism by which prolonging the dying process is associated with less peacefulness and the worst possible death. Alternatively, nurses may be more comfortable giving opioids for pain or providing anxiolysis with a DNR order in place, therefore an early DNR order may allow for improved symptom management at the end of life.

This is the first study, to our knowledge, to investigate the relationship between DNR timing and ICU patients' physical and psychological suffering, though the results must be examined in light of its strengths and weaknesses. Strengths include the multi-centered sampling and high rate of nurse participation, which increases the study's generalizability and limits selection bias, respectively. Weaknesses include retrospective evaluation of nurses' assessments of patient experience in the last week of life. Because this study interviewed nurses in the weeks after a patient for whom they cared had died in the ICU, recall bias may have affected nurses' ability to rate patient symptoms and suffering. Still, we have no reason to believe that recall bias would influence nurse perception of suffering as it relates to the decedents' DNR status. Another limitation of this study is the nurse-assessment of patient symptoms. While patients' own reporting of their symptoms would be preferable to nurse report, this approach was not feasible due to the observation that a majority of dying patients in the ICU are unable to communicate.[14] Further, earlier studies have demonstrated that nurses provide accurate

assessments of patients' symptoms and in-hospital outcomes at the end of life, especially compared to caregivers and physicians.[14, 19–23, 42] As noted above, this study included a sample of decedents in the ICU, but we recognize that in clinical practice it may be difficult to know precisely when patients will die. In patients with end-stage disease (e.g., advanced cancer) who have a high predicted mortality, our results suggest that an early approach to conversations about DNR status may reduce avoidable suffering.

In conclusion, early DNR, within the first 48 hours of ICU admission, for patients who die in the ICU is associated with fewer nonbeneficial procedures and lower odds of nurse-perceived loss of dignity, being not at peace, suffering and having had the worst possible death. The timing, not just the presence, of DNR orders may play an important role in patients' quality of death in the ICU.

Supporting information

S1 File. DNR data.csv.
(CSV)

S2 File. Quality of Life in the last week of life in the ICU _ REDCap.
(PDF)

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References

1. Jude JR, Kouwenhoven WB, Knickerbocker GG. Cardiac arrest. Report of application of external cardiac massage on 118 patients. *JAMA*. 1961; 178:1063–70. Epub 1961/12/16. <https://doi.org/10.1001/jama.1961.03040500005002> PMID: 14452697.
2. Bishop JP, Brothers KB, Perry JE, Ahmad A. Reviving the conversation around CPR/DNR. *Am J Bioeth*. 2010; 10(1):61–7. Epub 2010/01/16. <https://doi.org/10.1080/15265160903469328> PMID: 20077345.
3. Rabkin MT, Gillerman G, Rice NR. Orders not to resuscitate. *The New England journal of medicine*. 1976; 295(7):364–6. <https://doi.org/10.1056/NEJM197608122950705> PMID: 934225.
4. Chang DW, Brass EP. Patient and hospital-level characteristics associated with the use of do-not-resuscitate orders in patients hospitalized for sepsis. *Journal of general internal medicine*. 2014; 29(9):1256–62. Epub 2014/06/15. <https://doi.org/10.1007/s11606-014-2906-x> PMID: 24928264; PubMed Central PMCID: PMC4139525.

5. Burden E, Pollock L, Paget C. Quality of life after in-hospital cardiopulmonary resuscitation for patients over the age of 80 years. *Postgrad Med J*. 2019. Epub 2019/09/15. <https://doi.org/10.1136/postgradmedj-2019-136565> PMID: 31519712.
6. Tomlinson T, Brody H. Ethics and communication in do-not-resuscitate orders. *The New England journal of medicine*. 1988; 318(1):43–6. Epub 1988/01/07. <https://doi.org/10.1056/NEJM198801073180109> PMID: 3336383.
7. Richardson DK, Zive D, Daya M, Newgard CD. The impact of early do not resuscitate (DNR) orders on patient care and outcomes following resuscitation from out of hospital cardiac arrest. *Resuscitation*. 2013; 84(4):483–7. <https://doi.org/10.1016/j.resuscitation.2012.08.327> PMID: 22940596.
8. Teno JM, Gozalo PL, Bynum JW, et al. Change in end-of-life care for medicare beneficiaries: Site of death, place of care, and health care transitions in 2000, 2005, and 2009. *JAMA*. 2013; 309(5):470–7. <https://doi.org/10.1001/jama.2012.207624> PMID: 23385273
9. Covinsky KE, Fuller JD, Yaffe K, Johnston CB, Hamel MB, Lynn J, et al. Communication and decision-making in seriously ill patients: findings of the SUPPORT project. *The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments*. *Journal of the American Geriatrics Society*. 2000; 48(5 Suppl):S187–93. Epub 2000/05/16. <https://doi.org/10.1111/j.1532-5415.2000.tb03131.x> PMID: 10809474.
10. Morrell ED, Brown BP, Qi R, Drabiak K, Helft PR. The do-not-resuscitate order: associations with advance directives, physician specialty and documentation of discussion 15 years after the Patient Self-Determination Act. *J Med Ethics*. 2008; 34(9):642–7. <https://doi.org/10.1136/jme.2007.022517> PMID: 18757631.
11. Levin TT, Li Y, Weiner JS, Lewis F, Bartell A, Piercy J, et al. How do-not-resuscitate orders are utilized in cancer patients: timing relative to death and communication-training implications. *Palliative & supportive care*. 2008; 6(4):341–8. Epub 2008/11/14. <https://doi.org/10.1017/s1478951508000540> PMID: 19006588.
12. Alsirafy SA, Mohammed AA, Al-Zahrani AS, Raheem AA, El-Kashif AT. The Relation Between the Timing of Palliative Care and the Frequency and Timing of Do-Not-Resuscitate Orders Among Cancer Deaths in a Tertiary Care Hospital. *The American journal of hospice & palliative care*. 2015; 32(5):544–8. <https://doi.org/10.1177/1049909114529014> PMID: 24671030.
13. Araw AC, Araw AM, Pekmezaris R, Nouryan CN, Sison C, Tommasulo B, et al. Medical orders for life-sustaining treatment: Is it time yet? *Palliative & supportive care*. 2014; 12(2):101–5.
14. Su A, Lief L, Berlin D, Cooper Z, Ouyang D, Holmes J, et al. Beyond Pain: Nurses' Assessment of Patient Suffering, Dignity, and Dying in the Intensive Care Unit. *J Pain Symptom Manage*. 2018. <https://doi.org/10.1016/j.jpainsymman.2018.02.005> PMID: 29458082.
15. Jayes RL, Zimmerman JE, Wagner DP, Draper EA, Knaus WA. Do-not-resuscitate orders in intensive care units. Current practices and recent changes. *JAMA*. 1993; 270(18):2213–7. Epub 1993/11/10. PMID: 8411606.
16. Silvennoinen K, Meretoja A, Strbian D, Putaala J, Kaste M, Tatlisumak T. Do-not-resuscitate (DNR) orders in patients with intracerebral hemorrhage. *Int J Stroke*. 2014; 9(1):53–8. Epub 2013/10/24. <https://doi.org/10.1111/ijvs.12161> PMID: 24148872.
17. Sinuff T, Cook DJ, Rocker GM, Griffith LE, Walter SD, Fisher MM, et al. DNR directives are established early in mechanically ventilated intensive care unit patients. *Can J Anaesth*. 2004; 51(10):1034–41. Epub 2004/12/03. <https://doi.org/10.1007/BF03018494> PMID: 15574557.
18. Scheunemann LP, McDevitt M, Carson SS, Hanson LC. Randomized, controlled trials of interventions to improve communication in intensive care: a systematic review. *Chest*. 2011; 139(3):543–54. Epub 2010/11/26. <https://doi.org/10.1378/chest.10-0595> PMID: 21106660.
19. Zhang B, Nilsson ME, Prigerson HG. Factors important to patients' quality of life at the end of life. *Arch Intern Med*. 2012; 172(15):1133–42. <https://doi.org/10.1001/archinternmed.2012.2364> PMID: 22777380; PubMed Central PMCID: PMC3806298.
20. Detsky ME, Harhay MO, Bayard DF, Delman AM, Buehler AE, Kent SA, et al. Discriminative Accuracy of Physician and Nurse Predictions for Survival and Functional Outcomes 6 Months After an ICU Admission. *JAMA*. 2017; 317(21):2187–95. <https://doi.org/10.1001/jama.2017.4078> PMID: 28528347; PubMed Central PMCID: PMC5710341.
21. Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. *Journal of clinical epidemiology*. 2002; 55(11):1130–43. [https://doi.org/10.1016/s0895-4356\(02\)00479-1](https://doi.org/10.1016/s0895-4356(02)00479-1) PMID: 12507678.
22. Horton R. Differences in assessment of symptoms and quality of life between patients with advanced cancer and their specialist palliative care nurses in a home care setting. *Palliative medicine*. 2002; 16(6):488–94. <https://doi.org/10.1191/0269216302pm588oa> PMID: 12465695.

23. Nekolaichuk CL, Bruera E, Spachynski K, MacEachern T, Hanson J, Maguire TO. A comparison of patient and proxy symptom assessments in advanced cancer patients. *Palliative medicine*. 1999; 13(4):311–23. <https://doi.org/10.1191/026921699675854885> PMID: 10659100.
24. Mack JW, Nilsson M, Balboni T, Friedlander RJ, Block SD, Trice E, et al. Peace, Equanimity, and Acceptance in the Cancer Experience (PEACE): validation of a scale to assess acceptance and struggle with terminal illness. *Cancer*. 2008; 112(11):2509–17. Epub 2008/04/23. <https://doi.org/10.1002/cncr.23476> PMID: 18429006; PubMed Central PMCID: PMC3809101.
25. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2010; 28(7):1203–8. Epub 2010/02/04. <https://doi.org/10.1200/jco.2009.25.4672> PMID: 20124172; PubMed Central PMCID: PMC2834470.
26. Prigerson HG, Bao Y, Shah MA, Paulk ME, LeBlanc TW, Schneider BJ, et al. Chemotherapy Use, Performance Status, and Quality of Life at the End of Life. *JAMA oncology*. 2015; 1(6):778–84. Epub 2015/07/24. <https://doi.org/10.1001/jamaoncol.2015.2378> PMID: 26203912; PubMed Central PMCID: PMC4828728.
27. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2010; 28(29):4457–64. Epub 2010/09/15. <https://doi.org/10.1200/jco.2009.26.3863> PMID: 20837950; PubMed Central PMCID: PMC2988637.
28. Zingmond DS, Wenger NS. Regional and institutional variation in the initiation of early do-not-resuscitate orders. *Archives of internal medicine*. 2005; 165(15):1705–12. <https://doi.org/10.1001/archinte.165.15.1705> PMID: 16087817
29. Shepardson LB, Gordon HS, Ibrahim SA, Harper DL, Rosenthal GE. Racial Variation in the Use of Do-Not-Resuscitate Orders. *Journal of general internal medicine*. 1999; 14(1):15–20. <https://doi.org/10.1046/j.1525-1497.1999.00275.x> PMID: 9893086
30. Faigle R, Ziai WC, Urrutia VC, Cooper LA, Gottesman RF. Racial Differences in Palliative Care Use After Stroke in Majority-White, Minority-Serving, and Racially Integrated U.S. Hospitals. *Critical care medicine*. 2017; 45(12):2046–54. Epub 2017/10/19. <https://doi.org/10.1097/CCM.0000000000002762> PMID: 29040110; PubMed Central PMCID: PMC5693642.
31. Maxfield M, Kluck B, Greenberg J, Pyszczynski T, Cox CR, Solomon S, et al. Age-Related Differences in Responses to Thoughts of One's Own Death: Mortality Salience and Judgments of Moral Transgressions. *Psychology and aging*. 2007; 22(2):341–53. <https://doi.org/10.1037/0882-7974.22.2.341> PMC2396593. PMID: 17563189
32. Sharp T, Moran E, Kuhn I, Barclay S. Do the elderly have a voice? Advance care planning discussions with frail and older individuals: a systematic literature review and narrative synthesis. *Br J Gen Pract*. 2013; 63(615):e657–68. Epub 2013/10/25. <https://doi.org/10.3399/bjgp13X673667> PMID: 24152480; PubMed Central PMCID: PMC3782798.
33. Wenger NS, Pearson ML, Desmond KA, Harrison ER, Rubenstein LV, Rogers WH, et al. Epidemiology of do-not-resuscitate orders. Disparity by age, diagnosis, gender, race, and functional impairment. *Arch Intern Med*. 1995; 155(19):2056–62. PMID: 7575064.
34. Krakauer EL, Crenner C, Fox K. Barriers to optimum end-of-life care for minority patients. *Journal of the American Geriatrics Society*. 2002; 50(1):182–90. <https://doi.org/10.1046/j.1532-5415.2002.50027.x> PMID: 12028266.
35. Loggers ET, Maciejewski PK, Paulk E, DeSanto-Madeya S, Nilsson M, Viswanath K, et al. Racial differences in predictors of intensive end-of-life care in patients with advanced cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2009; 27(33):5559–64. Epub 2009/10/07. <https://doi.org/10.1200/JCO.2009.22.4733> PMID: 19805675; PubMed Central PMCID: PMC2792953.
36. Azoulay E, Pochard F, Kentish-Barnes N, Chevret S, Aboab J, Adrie C, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *American journal of respiratory and critical care medicine*. 2005; 171(9):987–94. Epub 2005/01/25. <https://doi.org/10.1164/rccm.200409-1295OC> PMID: 15665319.
37. Adelman RD, Tmanova LL, Delgado D, Dion S, Lachs MS. Caregiver burden: a clinical review. *JAMA*. 2014; 311(10):1052–60. Epub 2014/03/13. <https://doi.org/10.1001/jama.2014.304> PMID: 24618967.
38. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA*. 2008; 300(14):1665–73. <https://doi.org/10.1001/jama.300.14.1665> PMID: 18840840; PubMed Central PMCID: PMC2853806.

39. Sulmasy DP, Terry PB, Weisman CS, Miller DJ, Stallings RY, Vettese MA, et al. The accuracy of substituted judgments in patients with terminal diagnoses. *Annals of internal medicine*. 1998; 128(8):621–9. <https://doi.org/10.7326/0003-4819-128-8-199804150-00002> PMID: 9537935.
40. Loggers ET, Maciejewski PK, Jimenez R, Nilsson M, Paulk E, Stieglitz H, et al. Predictors of intensive end-of-life and hospice care in Latino and white advanced cancer patients. *Journal of palliative medicine*. 2013; 16(10):1249–54. Epub 2013/09/24. <https://doi.org/10.1089/jpm.2013.0164> PMID: 24053593; PubMed Central PMCID: PMC3791053.
41. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ*. 2010; 340. <https://doi.org/10.1136/bmj.c1345> PMID: 20332506
42. Downey L, Curtis JR, Lafferty WE, Herting JR, Engelberg RA. The Quality of Dying and Death Questionnaire (QODD): Empirical Domains and Theoretical Perspectives. *Journal of Pain and Symptom Management*. 2010; 39(1):9–22. <https://doi.org/10.1016/j.jpainsymman.2009.05.012> PMID: 19782530