Quantifying the Mortality Impact of Do-Not-Resuscitate Orders in the ICU*

Lior Fuchs, MD[1,2]; Matthew Anstey, MD, MPH[3]; Mengling Feng, PhD[4,5]; Ronen Toledano, MD[1]; Slava Kogan, BMedSci[1]; Michael D. Howell, MD, MPH[6]; Peter Clardy, MD[7]; Leo Celi, MD, MS, MPH[4,7]; Daniel Talmor, MD, MPH[2]; Victor Novack, MD, PhD[1,2]

Objectives: We quantified the 28-day mortality effect of preexisting do-not-resuscitate orders in ICUs.

Design: Longitudinal, retrospective study of patients admitted to five ICUs at a tertiary university medical center (Beth Israel Deaconess Medical Center, BIDMC, Boston, MA) between 2001 and 2008.

Intervention: None.

Patients: Two cohorts were defined: patients with do not resuscitate advance directives on day 1 of ICU admission and a control group comprising patients with no limitations of level of care on ICU day 1 (full code).

Measurements and Main Results: The primary outcome was mortality at 28 days after ICU admission. Of 19,007 ICU patients, 1,239 patients (6.5%) had a do-not-resuscitate order on the first day of ICU admission and survived 48 hours in the ICU. We matched those do-not-resuscitate patients with 2,402 patients with full-code status. Twenty-eight day and 1-year mortality were both significantly higher in the do-not-resuscitate group (33.9% vs 18.4% and 60.7% vs 40.2%; $p < 0.001$, respectively).

Conclusion: Do-not-resuscitate status is an independent risk factor for ICU mortality. This may reflect severity of illness not captured by other clinical factors, but the perceptions of the treating team related to do-not-resuscitate status could also be causally responsible for increased mortality in patients with do-not-resuscitate status. (*Crit Care Med* 2017; 45:1019–1027)

Key Words: advanced directives; do not resuscitate; mortality

***See also p. 1100**.

[1]Clinical Research Center, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

[2]Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA.

[3]Intensive Care Unit, Sir Charles Gairdner Hospital, Nedlands, Western Australia.

[4]The Harvard–MIT Division of Health Sciences & Technology, Massachusetts Institute of Technology, Cambridge, MA.

[5]Institute for Infocomm Research, Agency for Science, Technology and Research, Singapore.

[6]Center for Quality and the Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL.

[7]Department of Pulmonary and Critical Care Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Drs. Fuchs, Anstey, and Novack contributed in study concept, design and drafting of the article. Drs. Fuchs, Anstey, Feng, Toledano, Kogan, Howell, Clardy, Celli, Talmor, and Novack contributed in acquisition, analysis, or interpretation of data. Drs. Toledano, Kogan, and Novack contributed in statistical analysis.

Dr. Anstey received funding from Choosing Wisely Australia (advisory board member). Dr. Feng disclosed work for hire. Dr. Howell received funding from UpToDate (royalties). Dr. Celi received support for article research from National Institutes of Health. Dr. Novack received funding from Cardiomed Consultants LLC. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: victorno@clalit.org.il

DOI: 10.1097/CCM.0000000000002312

Nearly half of all Americans die in the hospital, and up to 30% of chronically ill Medicare beneficiaries are admitted to the ICU during their final hospital admission (1). Although almost 60 million Americans have a living will, explicit resuscitation directives are not common (2, 3). When such directives are in place, their effects on patient outcomes are unclear.

When the American Heart Association first approved the clinical use of cardiopulmonary resuscitation (CPR), it also proposed that withholding or withdrawing CPR is ethically appropriate if the anticipated harm outweighs the benefit (4). However since then, the terminology and interpretation of the "code status" of a patient has become complicated and confusing. Strictly speaking, do not resuscitate (DNR) means "in the event of cardiac arrest, do not provide CPR" and should not be mistaken with the decision not to provide treatment to the patient (5). Practically, DNR has been interpreted in a broad range from "do not perform CPR in the event of cardiac arrest" to "do not treat this patient aggressively if they deteriorate" and "not for active treatment" (6). Thus, clinicians may interpret a DNR order to be consistent with a decrease in the intensity of care to be provided to these patients (7–9).

Most patients with DNR orders fit into two groups. The first group is those with a DNR directive at or prior to admission. In this group of patients, there is the expectation to receive the same level of care but not the CPR if they have a cardiac arrest. The second group consists of patients in whom the DNR directive is applied later during the hospital stay, possibly due to lack of response to therapy or a change in clinical status. In these patients, DNR is often a marker of the severity of their illness or deteriorating condition (10). Previous research has not distinguished between these two groups, which may account for the discrepant results of DNR status and hospital mortality analyses in surgical populations (11, 12). In a general hospital population, Escobar et al (13) found that an admission order for restricted resuscitation was a mortality risk factor in the general hospital population but little research has focused on the ICU population.

In this study, we sought to measure the effect of pre-ICU admission DNR order on 28-day mortality. We hypothesize that preadmission DNR status is an independent mortality risk factor. Specifically, we evaluated the mortality risk associated with DNR status adjusted for the severity of the disease and lifesaving interventions.

MATERIALS AND METHODS

Using the Multi Parameter Intelligent Monitoring of Intensive Care II database (14, 15), we conducted a longitudinal, single-center, retrospective study analyzing 19,007 patients admitted to five ICUs at a tertiary university medical center (Beth Israel Deaconess Medical Center, BIDMC, Boston, MA) between the years 2001 and 2008.

The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center and was granted a waiver of informed consent.

Assembly of the Cohort

We included patients above the age of 18 who were hospitalized in three medical ICUs and two surgical and trauma ICUs with total of 58 ICU beds. At BIDMC, completion of a resuscitation status order is obligatory at ICU admission, with the default order being "full code." The form contains a list of the possible ICU interventions, their benefits, and alternatives. The patient or proxy can then consent to these options, or not, which can result in the selection of the DNR (do not perform CPR in the event of cardiac arrest) option. If the DNR option is selected, the attending physician is notified by electronic alert. Patients who did not survive the first 48 hours of ICU admission were excluded.

Two cohorts were defined: patients with DNR code status on day 1 of ICU admission and patients with full code on day 1, regardless of their code status later during the admission, as the control group (matched 1:2). The matching of these two cohorts was based on age at admission (± 3 yr), type of ICU (medical/surgical), and probability for death at 28 days (caliper width 0.05). Patients with other treatment restrictions on ICU admission, such as do not intubate or comfort measures only (CMO), were excluded.

Outcomes Measurement

The primary outcome was short-term mortality at 28 days from ICU admission. The secondary outcome was mortality at 1 year from ICU admission for those who survived 28 days from ICU admission. Also, we have measured number of radiology reports per admission day standardized to length of stay, number of medications prescribed, and number of laboratory tests taken per person in both groups.

Statistical Analysis

The baseline descriptive statistics of the cohort were based on frequency distributions for categorical data and means and SDs or medians and interquartile ranges for continuous data, according to normality. Univariate group comparisons for continuous data were done using student *t* test or nonparametric Mann-Whitney *U* tests, as appropriate, and χ^2 or Fisher exact tests for categorical data. Continuous variables included age, Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) severity of disease scores at admission (16, 17), and Elixhauser comorbidity score (18).

For analysis of 28-day mortality, a multivariable logistic regression model was developed using the full-code cohort. Variables adjusted for in the final model were selected based on the statistical and clinical significance and included gender, age, living with spouse at home, reason for hospitalization (grouped by systems, i.e., cardiovascular, respiratory), comorbidities, SOFA score, Elixhauser score, and life-sustaining treatment during hospitalization (renal replacement therapy, ventilation, and vasopressors). Regression coefficients from the full-code mortality model were used to calculate a predicted probability of death for each patient in the DNR group. Each cohort (full code/DNR) was divided by deciles of mortality probabilities and for each decile, we reported the observed 28-day mortality rate. We graphically represented the observed and expected 28-day mortality by deciles, within the DNR and non-DNR groups. Finally, we calculated the standardized mortality index for each DNR group decile (equal to the observed mortality rate divided by the average expected mortality). To compare patients who chose DNR status on arrival to the ICU with those who started as full code, we have matched the cohorts (1:2) by age, type of ICU unit, and probability of death in 28 days (caliper 0.05). Furthermore, we added two sensitivity analyses to investigate if the DNR effect is consistent. In the first sensitivity analysis, we excluded all patients with diagnosis of the malignancy. For the second sensitivity analysis, we have calculated the propensity score for DNR on ICU admission. Propensity score was calculated based on the logistic regression model inclusive of: unit (medical/ surgical), gender, age, marital status, presence of diabetes, congestive heart failure, alcohol abuse, cardiac arrhythmias, valvular diseases, hypertension, renal failure, chronic pulmonary diseases, liver disease, cancer, psychological disease, reason for hospitalization (cardiovascular, respiratory, cancer, gastro intestinal, genitourinary, trauma), and SAPS score. Then we matched patients with DNR on the first day with those without limitation of care (1:2) on probability to die in 28 days (caliper width 0.05), calculated propensity score (caliper width 0.10), age (± 3 yr), and type of ICU unit (medical/surgical). For analysis of 1-year survival, among those who survived 28 days (landmark analysis), we used a Cox proportional hazards regression model using the same variables as for the 28-day calculation.

For the DNR cohort, we calculated the standardized mortality rate (SMR) at 28 days and at 1 year for those who survived to 28 days. The SMR was adjusted for age above 65, gender, type of ICU (surgical vs medical ICU), presence of metastatic cancer, and use of mechanical ventilation.

All reported p values were rounded to two decimal places. Data were analyzed using STATA 12.1 (Stata Corp., College Station, TX) and SPSS 20 software (IBM, Armonk, NY). All statistical tests and/or CIs, as appropriate, were performed at $\alpha = 0.05$ (two-sided).

RESULTS

Patient Population

Of 19,007 ICU patients, 1,239 patients (6.5%) had a DNR order on the first day of ICU admission and survived at least 48 hours (**Fig. 1**). We matched those patients (1:2, by age, type of ICU, and 28-d probability of death) with 2,402 patients with no limitation of care on ICU day 1 (full code). Before matching, 7.4% (1,265/16,987) of non-DNR patients later received DNR orders. After matching, the proportion changed and 15.9% (330/2,072) of non-DNR patients became DNR during their ICU stay.

Table 1 depicts the baseline and hospital characteristics of the two matched groups. Overall morbidity burden (Elixhauser comorbidity score) was not significantly different between the groups.

The primary reasons for admission were similarly distributed between the groups, with the exception of a cancer-related admission being more frequent in DNR patients. Illness severity at ICU admission, as calculated by the SOFA score, was not significantly different between the groups. The utilization of renal replacement therapy and vasopressors did not differ between the groups, but DNR patients were less likely to receive mechanical ventilation (31.3% vs 44.2%; $p < 0.001$).

Investigations Performed

Patients with DNR order on day 1 received less number of radiology reports per admission day standardized to length of stay (0.31 [95% CI, 0–0.63] vs 0.42 [95% CI, 0–0.69]; $p = 0.003$) as well as less number of medications prescribed (47.4 [95% CI, 35.4–62.7] vs 56.8 [95% CI, 42.3–74.8]; $p < 0.0001$), whereas number of laboratory tests taken per person were not significantly different (7.37 [95% CI, 4.31–10.59] vs 7.26 [95% CI, 4.72–10.6]; $p = 0.64$).

Mortality Analysis

Twenty-eight day and one-year mortality were both significantly higher in the DNR group (33.9% vs 18.4% and

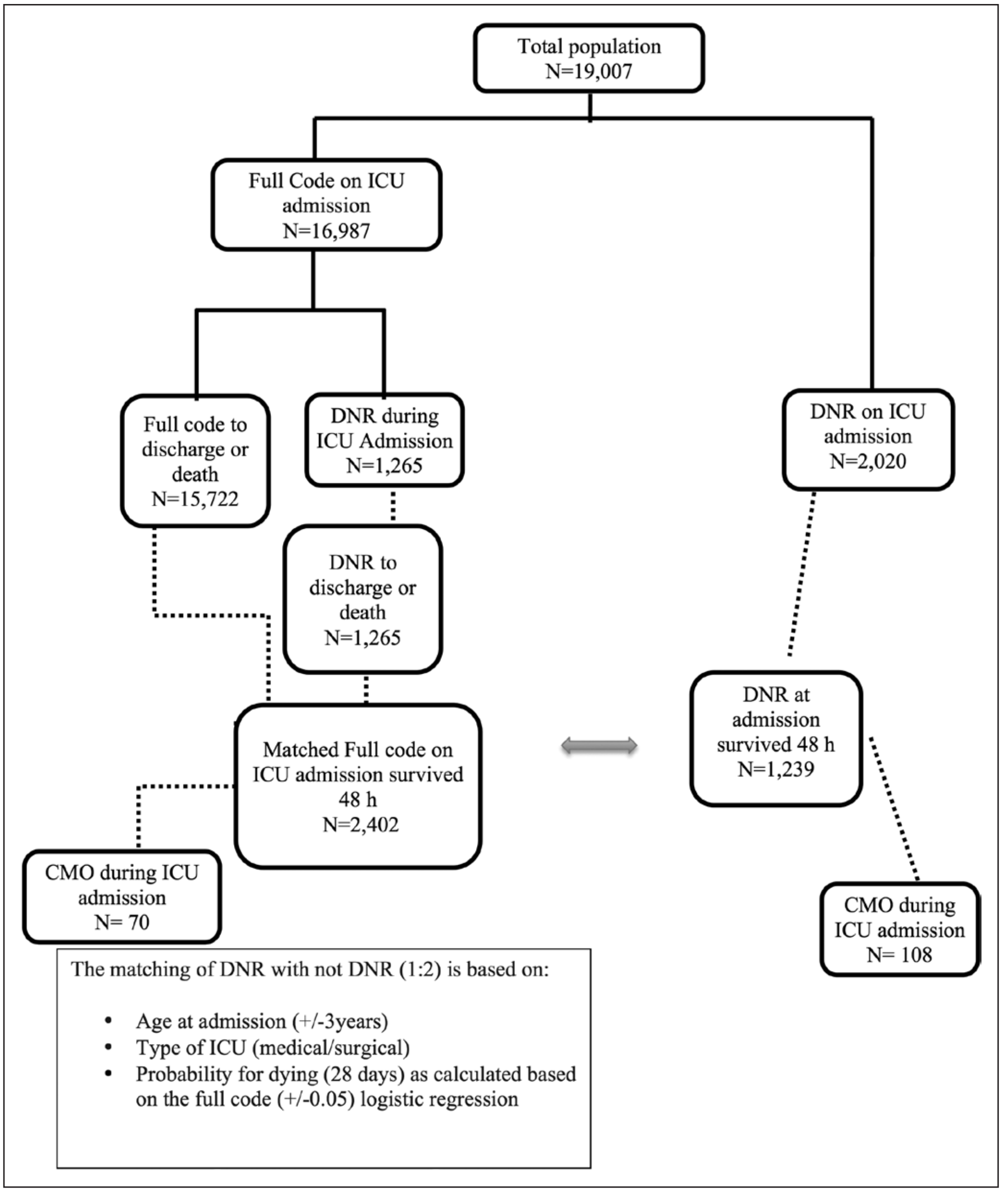


Figure 1. Study population flowchart. CMO = comfort measures only, DNR = do not resuscitate.

TABLE 1. Baseline Characteristics of ICU Patients and Hospitalization Characteristics ($n = 3,641$)

Variables		Code Status: Full Code on ICU Day 1 ($n = 2,402$)	Code Status: Do Not Resuscitate on Day 1 ($n = 1,239$)	p
Type of ICU, n (%)	Medical (medical, mixed medical/surgical)	1,947 (81.1)	1,010 (81.5)	0.73
	Surgical (surgical, cardiac-surgical)	455 (18.9)	229 (18.5)	
Male gender, n (%)		1,222 (50.9)	510 (41.2)	< 0.001
Age, yr (± SD)		76.63 (± 13.05)	77.24 (± 13.30)	0.18
Live with spouse, n (%)		1,117 (46.5)	433 (34.9)	< 0.001
Comorbidities, n (%)	Elixhauser score 28 d, median (IQR)	6 (1–10)	6 (3–11)	< 0.001
	Congestive heart failure	918 (38.2)	483 (39.0)	0.65
	Chronic renal failure	246 (10.2)	123 (9.9)	0.76
	Metastatic cancer	121 (5.0)	107 (8.6)	< 0.001
	Psychiatric disease (psychosis or depression)	153(6.4)	122(9.8)	< 0.001
	Diabetes mellitus	579 (24.1)	299 (24.1)	0.98
	Alcohol abuse	65 (2.7)	24 (1.9)	0.15
	Cardiac arrhythmias	858 (35.7)	404 (32.6)	0.06
	Valvular disease	299 (12.4)	145 (11.7)	0.51
	Hypertension	887 (36.9)	420 (33.9)	0.07
	Chronic pulmonary disease	553 (23.0)	294 (23.7)	0.63
	Liver disease	96 (4.0)	56 (4.5)	0.45
Admission source, n (%)	Emergency department	1,836 (76.4)	1,002 (80.9)	0.002
Primary reason of admission, n (%)	Cardiovascular	419 (17.4)	211 (17.0)	0.75
	Respiratory	438 (18.2)	201 (16.2)	0.13
	Cancer	514 (21.4)	329 (26.6)	< 0.001
	Gastrointestinal	414 (17.2)	193 (15.6)	0.20
	Trauma	384 (16.0)	176 (14.2)	0.16
Acuity score at admission	Sequential Organ Failure Assessment, median (IQR)	5 (2–8)	4 (3–7)	0.40
	Simplified Acute Physiology Score I, median (IQR)	14 (11–17)	14 (11–17)	0.96
Intensity of care n (%)	Renal replacement therapy during hospitalization	236 (9.8)	103 (8.3)	0.14
	Use of vasopressors	634 (26.4)	295 (23.8)	0.09
	Mechanical ventilation	1,061 (44.2)	388 (31.3)	< 0.001

IQR = interquartile range.

60.7% vs 40.2%; $p < 0.001$, respectively), with the two groups diverging sharply after the first few days (**Fig. 2A**). Between 28 days and 6 months, an additional 14.8% of patients died in the full-code group versus 20% in DNR group. During the next 6 months (6–12 mo following the admission), mortality rates increased by 5% in both groups to reach 60.7% versus 40.2% in the DNR and full-code cohorts, respectively, at 1 year ($p < 0.001$).

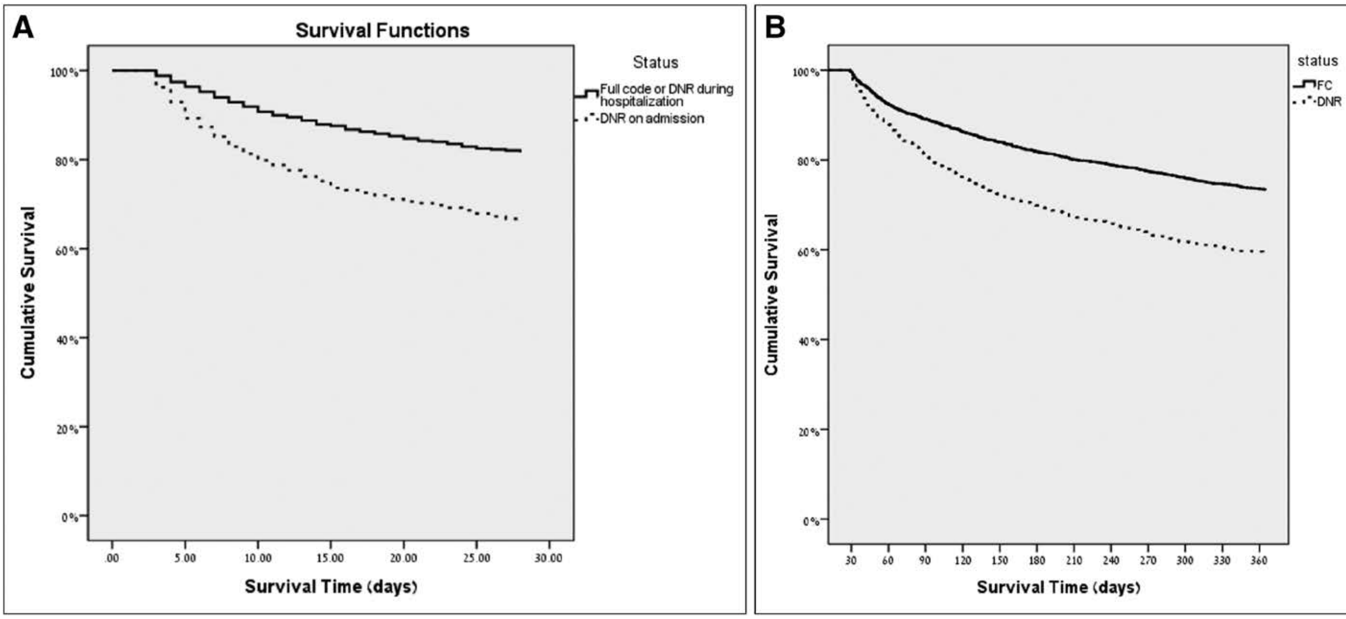


Figure 2. A, Twenty-eight days survival for patients survived first 48 hr of hospitalization. **B**, Landmark analysis. Kaplan-Meier 1-yr survival curves for patient surviving first 28 d. DNR = do not resuscitate.

Standardized Short-Term Mortality Index

We developed a prediction model for 28-day survival among full-code patients who survived at least 48 hours in the ICU (**Table 2**). **Figure 3*A*** shows the prediction accuracy of the model among non-DNR patients. Hosmer-Lemeshow chi-square statistic was 13.05, *p* value equals to 0.11, and *C*-statistic was 0.76 (95% CI, 0.73–0.80). We divided the full-code cohort into deciles and calculated the average expected mortality probability and the observed mortality rate for each decile. Figure 3*A* shows that the difference between the expected and observed mortality was minimal across all mortality risk deciles. Overall, the mortality index (observed/expected) in the full-code cohort was 0.99 (95% CI, 0.37–5.59).

Subsequently, we calculated the expected 28-day mortality probability for the DNR group based on the full-code cohort model. Figure 3***B*** presents the expected and observed mortality across deciles of the expected mortality risk. The overall 28-day standardized mortality index for DNR cohort was 1.98 (95% CI, 0.73–10.22). We divided patients into deciles based on predicted risk of death from our full risk-prediction models. In sicker patients (those with higher probability of death), the impact of DNR diminished. Relative risk decreased from 5.44 (95% CI, 3.79–13.37) in the lowest risk decile to 1.15 (95% CI, 0.80–1.48) in the highest risk decile.

Furthermore, we calculated two new SMRs to separate between the DNR as a marker of the severity versus DNR as a partial cause of the increased mortality. Thus, we added two sensitivity analyses. The first sensitivity analysis included 3,641 patients from the original cohort, and the 960 with cancer were excluded. Subsequently, we calculated the SMR on all 2,681 patients with no cancer history (1,833 full-code patients and 848 DNR patients). The mortality index graphs behave similarly to the original study group. The mortality index (observed/expected) in the full-code cohort is 1.00 (95% CI, 0.37–5.00). The overall 28-day standardized mortality index for DNR cohort was 2.21 (95% CI, 0.91–10.33).

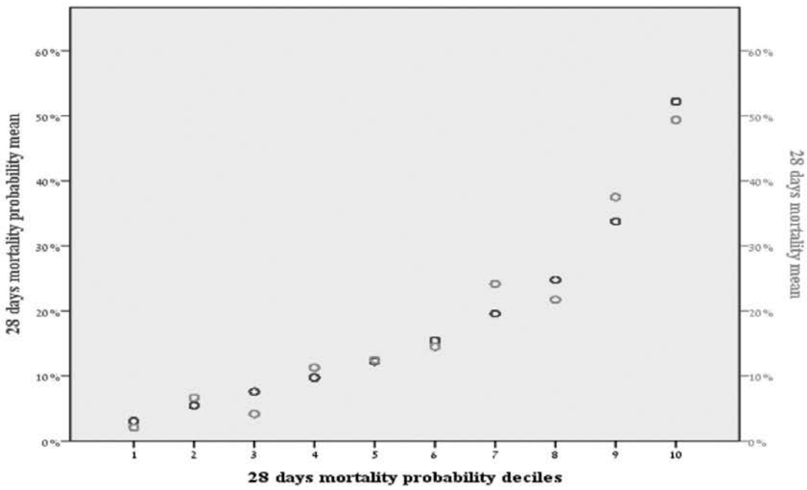
Finally, we have matched the cohorts using the same variables as in the former analysis and added propensity score. After matching, the analysis included 3,051 patients: 2,034 full code and 1,017 DNR patients. The mortality index (observed/expected) in the full-code cohort was 1.33 (95% CI, 0.38–5.33). The overall 28-day standardized mortality index for DNR cohort was 3.00 (95% CI, 0.86–11.00).

Supplemental digital content-Figure 4a (Supplemental Digital Content 1, http://links.lww.com/CCM/C372) shows DNR status association with 28-day mortality in various patient subgroups. Patients who were ventilated, hospitalized following a surgical procedure, or were free from metastatic cancer had the highest standardized mortality indices for DNR patients. In women, DNR status was associated with higher mortality when compared with men: standardized mortality ratio of 2.20 (95% CI, 2.09–2.32) versus 1.65 (95% CI, 1.55–1.75), respectively, *p* value of less than 0.001.

Landmark Analysis of 1-Year Mortality

Eight hundred nineteen of 1,239 DNR patients (66.1%) survived to 28 days, whereas 1,960 patients (81.6%) survived in the full-code group. Among the 28-day survivors, the 1-year Kaplan-Meier survival rates were 59.5% and 73.3% in the DNR and full-code cohorts, respectively (Fig. 2***B***). Cox proportional hazards regression model revealed that after adjustment for gender, type of ICU, age, living with a spouse at home, and comorbidities, the hazard ratio for 1-year mortality was 1.65 (95% CI, 1.4–1.9) for DNR status on ICU admission compared with full-code patients ($p < 0.001$) (**Table 3**).

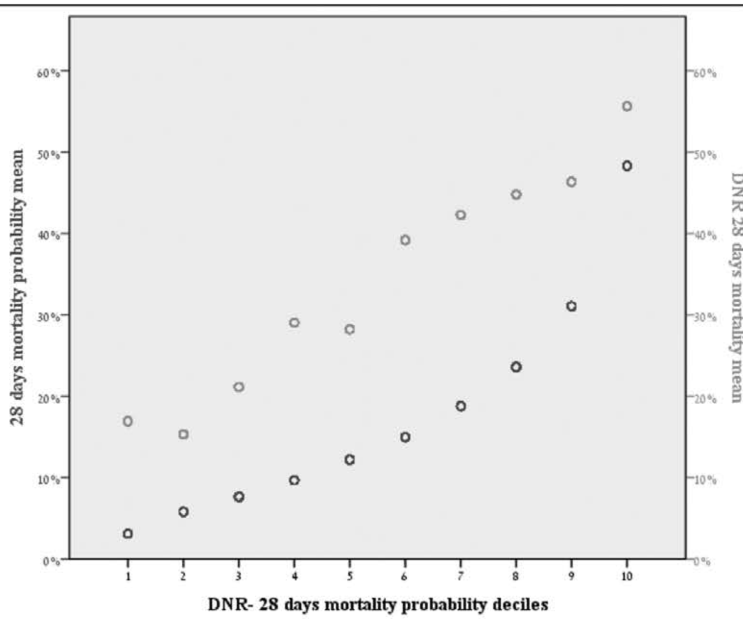
A



Green dots- Observed mortality rate: **Blue dots-** Predicted mortality rate
Standardized mortality rates:

	Deciles	1	2	3	4	5	6	7	8	9	10	all
	observed	0.02	0.06	0.04	0.11	0.12	0.14	0.24	0.22	0.37	0.49	0.22
	expected	0.03 (0.01-0.04)	0.05 (0.04-0.06)	0.07 (0.06-0.08)	0.09 (0.08-0.10)	0.12 (0.11-0.14)	0.15 (0.14-0.17)	0.19 (0.17-0.22)	0.25 (0.22-0.28)	0.34 (0.29-0.39)	0.52 (0.40-0.72)	0.18 (0.03-0.49)
Full Code	mortality index	0.68 (0.47-1.91)	1.22 (1.06-1.43)	0.54 (0.48-0.63)	1.15 (1.05-1.29)	1.01 (0.91-1.13)	0.93 (0.84-1.40)	1.23 (1.11-1.37)	0.88 (0.77-0.98)	1.11 (0.95-1.16)	0.94 (0.67-1.21)	0.99 (0.37-5.59)

B



Green dots- mortality rate; **Blue dots-** Predicted mortality rate by Full Code and DNR during hospitalization patients

Standardized mortality rates:

	Deciles	1	2	3	4	5	6	7	8	9	10	all
	observed	0.17	0.15	0.21	0.29	0.28	0.39	0.42	0.45	0.46	0.55	0.34
	expected	0.03 (0.01-0.04)	0.06 (0.05-0.07)	0.08 (0.07-0.08)	0.10 (0.08-0.10)	0.12 (0.11-0.13)	0.15 (0.13-0.16)	0.18 (0.16-0.20)	0.23 (0.21-0.26)	0.31 (0.27-0.36)	0.48 (0.37-0.69)	0.17 (0.03-0.45)
DNR	mortality index	5.44 (3.79-13.37)	2.65 (2.28-3.15)	2.76 (2.51-3.07)	3.01 (2.67-3.38)	2.31 (2.12-2.52)	2.61 (2.37-2.89)	2.25 (2.04-2.51)	1.89 (1.70-2.12)	1.49 (1.28-1.71)	1.15 (0.80-1.48)	1.93 (0.73-10.22)

Figure 3. A, Observed and expected 28-d mortality in patients with "full code" or "do not resuscitate (DNR) during hospitalization" who survived first 48 hr of ICU hospitalization. **B**, Twenty-eight days mortality for DNR at admission patients survived first 48 hr of ICU hospitalization.

Supplemental digital content-Figure 4b (Supplemental Digital Content 1, http://links.lww.com/CCM/C372) shows that within the DNR cohort, 1-year mortality did not differ much between various patient subgroups.

DISCUSSION

In this analysis, we have shown that "DNR" code status on day 1 of ICU admission is an independent predictor for 28-day mortality when adjusted for a variety of demographic, health, and acute treatment characteristics. The relative mortality risk associated with DNR status was the highest among the lower mortality risk group.

Our results are supported by previous observations. A number of studies showed that patients with DNR status in different clinical scenarios had higher mortality rates, longer length of stay, less chances to be admitted to intensive care, and higher complication rates (10, 12, 13, 19). However, the current study is the first to report on DNR association with mortality in the cohort of patients admitted to the ICUs.

Randomized control trials are the gold standard for establishing the causality. Yet, such a trial for assessing the effect of DNR status on mortality would be ethically impossible. Therefore, to answer this important clinical question, we are forced to use an observational study paradigm. Specifically, in our study, we aimed to show that DNR status is not merely a marker for the severity of the disease, but rather an independent mortality risk factor. To assure the study results validity, we used a number of approaches. First, in the study hospital, resuscitation status is an obligatory requirement for all ICU hospitalized patients. Second, we included patients with DNR status set on the first day of ICU admission and we included patients who obtained DNR status later during ICU stay in the control group (full-code group).

TABLE 2. Logistic Regression for 28-D Mortality in Patients Who Were Full Code at ICU Day 1

Variables		OR	95% CI Lower	95% CI Upper	p
Male gender		1.20	0.94	1.53	0.15
Age at admission (per yr)		1.03	1.02	1.04	< 0.001
Live with spouse		1.09	0.85	1.38	0.50
Reason of admission	Cardiovascular	1.83	0.97	3.47	0.06
	Respiratory	1.68	0.89	3.16	0.11
	Cancer	1.92	1.03	3.58	0.04
	Endocrine metabolic	0.66	0.17	2.56	0.55
	Gastrointestinal	0.88	0.45	1.72	0.71
	Genitourinary	1.20	0.49	2.96	0.69
	Trauma	1.23	0.64	2.36	0.52
Comorbidities	Diabetes	0.75	0.56	1.00	0.05
	Congestive heart failure	1.04	0.78	1.38	0.79
	Alcohol abuse	2.32	1.17	4.59	0.02
	Cardiac arrhythmias	1.25	0.96	1.63	0.10
	Valvular disease	0.87	0.61	1.24	0.45
	Hypertension	0.87	0.67	1.12	0.29
	Renal failure	1.25	0.83	1.88	0.28
	Chronic pulmonary	0.91	0.69	1.12	0.49
	Liver disease	1.58	0.89	2.80	0.12
	Metastatic cancer	2.80	1.66	4.73	< 0.001
	Psychosis	1.72	0.81	3.63	0.15
	Depression	0.32	0.12	0.83	0.02
Sequential Organ Failure Assessment score (per point)		1.07	1.03	1.12	0.001
Intensity of care	Renal replacement therapy during hospitalization	1.13	0.75	1.69	0.56
	Use of vasopressors	1.78	1.35	2.34	< 0.001
	Mechanical ventilation	1.62	1.21	2.16	0.001
Elixhauser score 28 d		1.04	1.01	1.07	0.012

OR = odds ratio.

Finally, we have excluded patients not surviving first 48 hours. These three measures minimized the selection bias that could be associated with DNR status.

We demonstrated that DNR code status is associated with higher mortality in the short term when compared with 1 year. If DNR status had been a pure marker of the disease severity, one would expect a similar effect on both short- and long-term mortalities. In other words, DNR assignment is not simply an identification of terminally sick patients dying either during the hospital stay or shortly afterwards. In addition, it seems that less sick patients had higher mortality risk associated with the DNR status.

A DNR order is a method of ensuring standardized communication for all clinicians, but physicians may erroneously associate DNR order with less aggressive treatment and may potentially alter the course of treatment. The DNR order, which practically means—do not perform CPR, but only when "nothing else can be done for me," may be confused with less aggressive or even palliative care in much earlier phase of care (6, 20). Beach and Morrison (21), using case scenarios, found that physicians "agreed" and "strongly agreed" to initiate fewer interventions when a DNR order was present. For example, patients with an acute decompensated heart failure

TABLE 3. Parsimonious Cox Proportional Hazards Mortality Models for Patients Who Survived First 28 d.

Variables	Hazard Ratio	95% CI Lower Bound	95% CI Upper Bound	*p*
Do not resuscitate vs full code	1.65	1.43	1.89	< 0.001
Reason of admission gastrointestinal	0.76	0.62	0.92	0.005
Reason of admission genitourinary	0.62	0.42	0.93	0.02
Chronic heart failure	1.24	1.05	1.45	0.01
Hypertension	0.72	0.62	0.84	< 0.001
Metastatic cancer	1.70	1.26	2.30	0.001
Renal replacement therapy	1.74	1.40	2.17	< 0.001
Ventilation	1.31	1.14	1.51	< 0.001
Elixhouser	1.02	1.01	1.03	0.007
Age	1.02	1.01	1.03	< 0.001

Adjusted for: Gender, type of ICU, age, live with spouse, diabetes mellitus, congestive heart failure, alcohol abuse, cardiac arrhythmias, valvular disease, hypertension, renal failure, chronic pulmonary, liver disease, metastatic cancer, major psychiatric disorder (psychosis or depression).

and DNR status were less likely to receive pharmacologic and nonpharmacologic heart failure interventions compared with non-DNR patients (22). Conversely, Kish Wallace et al (23) found that an advance directive did not influence the use of ICU interventions among critically ill cancer patients.

Patients in the ICU should have the autonomy to decide whether they want CPR or not. This decision should not affect the level of care, that is, we believe that patients, signing DNR order, should know that their chances to survive an ICU admission are equal to patient with similar severity of disease and no limitations of care except for the situation where there is a need for CPR. Our results show that there is a need for a better alignment between the patient wishes and treatment plan and intensity. A DNR order does not mean do not ventilate nor "treat the patient less." Our DNR patients received less mechanical ventilation, less radiologic investigations, and medications.

We believe that the binary choice between DNR and unlimited level of care does not provide enough direction to the care providers and is unclear to patients and their families. One of the proposals to achieve better granularity of the advanced live support directives included creation of the scale of treatment intensity: terminal, palliative, usual, and intensive with CPR included in the last group only (24). Other much more detailed advance directives as the Medical Orders for Life-Sustaining Treatment (MOLST) and Physician Order for Life-Sustaining Treatment (POLST) were proposed (25, 26). We intend to study further the impact of these detailed advanced directives on ICU outcomes from 2008 to date.

The TRIAD III trial suggested that many emergency physicians mistakenly associate living wills as DNR orders, and furthermore they often associate DNR orders with end-of-life care. Their survey showed that adding extra contextual information about the patient assisted in resolving the misinterpretation (27, 28).

We have shown that the association of DNR status and 28-day mortality is heterogeneous. It appears that women, surgical, mechanically ventilated, and oncologic patients with no metastases are particularly vulnerable groups. This finding suggests that the treating team alters the intensity of treatment provided, potentially as a result of personal perceptions of the patient characteristics. In particular, DNR association with mortality was 50% higher in women when compared with men. This gender association warrants additional investigation.

More than 40% of DNR patients who are admitted to the ICU survive to 1 year. The 1-year mortality outcome for patients surviving the first 28 days shows a significant separation between the full-code and DNR groups. This may be a residual effect of less treatment in the DNR group when they were hospitalized. Conversely, it may be that these patients with DNR orders are at higher risk of death in the medium term, and that some limitation in treatment is appropriate. Better defining these patient populations is a challenge for future studies.

Another explanation for the association between DNR code status at admission and higher mortality may be related to the readiness of DNR patients and families to discuss treatment deescalation through ICU stay. We found three times higher CMO code status prevalence for patients who were admitted as DNR patients (108/1,239 [8.7%]) compared with prevalence of CMO code status after full code on ICU admission (70/2,402 [2.9%]).

Our analysis has several important limitations. This was a single-center retrospective study, and thus its generalizability can be limited. The rate of DNR on ICU admission (2,020/19,439 [10%]) was similar to other reported rates (29–31). Despite the matching and adjustment, residual selection bias could still be present. We had data on neither cause of death nor palliative care involvement. A palliative care specialist service was available for consult at that time of the study. While we know anecdotally that it was used, unfortunately the database does not contain the referrals to palliative care and thus we do not have individual patient data for this element. We believe that the availability of this service may increase conversion from DNR to CMO. We could not assess quality of life among our ICU survivors.

We excluded patients who died within 48 hours from ICU admission. We think that exclusion of these patients resulted in a more conservative estimate of the DNR association with mortality by minimizing the selection bias. Yet, this exclusion can be associated with a different selection bias: patients with advanced directive prior to admission could be removed from the analysis. Unfortunately, we do not possess the data regarding the timing of the prior to admission advanced directive signing. Lastly, we cannot exclude that the excess mortality observed in the DNR cohort was partially due to the proper implementation of the order—DNR—when CPR was warranted.

CONCLUSIONS

DNR status seems to be independently associated with 28-day mortality in patients hospitalized in ICUs with a particularly high mortality risk in a number of patients subgroups. It might be hypothesized that the discrepancy in understanding of the DNR order by the treating team can be partially responsible for the observed association. Increased clarity of advanced live support directives could facilitate better alignment between the patient wishes and level of care to be provided by the clinicians.

REFERENCES

1. Centers for Disease Control and Prevention (CDC): Vital signs: Avoidable deaths from heart disease, stroke, and hypertensive disease–United States, 2001–2010. *MMWR Morb Mortal Wkly Rep* 2013; 62:721–727
2. Cook DJ, Guyatt G, Rocker G, et al: Cardiopulmonary resuscitation directives on admission to intensive-care unit: An international observational study. *Lancet* 2001; 358:1941–1945
3. Street M, Ottmann G, Johnstone MJ, et al: Advance care planning for older people in Australia presenting to the emergency department from the community or residential aged care facilities. *Health Soc Care Community* 2015; 23:513–522
4. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). I. Introduction. *JAMA* 1974; 227(Suppl):837–840
5. Kierzek G, Rac V: DNR and advance directives: International perspective. *Health Aff (Millwood)* 2010; 29:1080
6. Chen YY, Gordon NH, Connors AF, et al: Two distinct do-not-resuscitate protocols leaving less to the imagination: An observational study using propensity score matching. *BMC Med* 2014; 12:146
7. Phillips RS, Wenger NS, Teno J, et al: Choices of seriously ill patients about cardiopulmonary resuscitation: Correlates and outcomes. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *Am J Med* 1996; 100:128–137
8. Jonsson PV, McNamee M, Campion EW: The ‘Do not resuscitate’ order. A profile of its changing use. *Arch Intern Med* 1988; 148:2373–2375
9. Henneman EA, Baird B, Bellamy PE, et al: Effect of do-not-resuscitate orders on the nursing care of critically ill patients. *Am J Crit Care* 1994; 3:467–472
10. Wenger NS, Pearson ML, Desmond KA, et al: Outcomes of patients with do-not-resuscitate orders. Toward an understanding of what do-not-resuscitate orders mean and how they affect patients. *Arch Intern Med* 1995; 155:2063–2068
11. Saager L, Kurz A, Deogaonkar A, et al: Pre-existing do-not-resuscitate orders are not associated with increased postoperative morbidity at 30 days in surgical patients. *Crit Care Med* 2011; 39:1036–1041
12. Kazaure H, Roman S, Sosa JA: High mortality in surgical patients with do-not-resuscitate orders: Analysis of 8256 patients. *Arch Surg* 2011; 146:922–928
13. Escobar GJ, Gardner MN, Greene JD, et al: Risk-adjusting hospital mortality using a comprehensive electronic record in an integrated health care delivery system. *Med Care* 2013; 51:446–453
14. Saeed M, Lieu C, Raber G, et al: MIMIC II: A massive temporal ICU patient database to support research in intelligent patient monitoring. *Comput Cardiol* 2002; 29:641–644
15. Saeed M, Villarroel M, Reisner AT, et al: Multiparameter intelligent monitoring in intensive care II: A public-access intensive care unit database. *Crit Care Med* 2011; 39:952–960
16. Le Gall JR, Loirat P, Alperovitch A, et al: A Simplified Acute Physiology Score for ICU patients. *Crit Care Med* 1984; 12:975–977
17. Arts DG, de Keizer NF, Vroom MB, et al: Reliability and accuracy of Sequential Organ Failure Assessment (SOFA) scoring. *Crit Care Med* 2005; 33:1988–1993
18. van Walraven C, Austin PC, Jennings A, et al: A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009; 47:626–633
19. Shepardson LB, Youngner SJ, Speroff T, et al: Increased risk of death in patients with do-not-resuscitate orders. *Med Care* 1999; 37:727–737
20. Venneman SS, Narnor-Harris P, Perish M, et al: “Allow natural death” versus “do not resuscitate”: Three words that can change a life. *J Med Ethics* 2008; 34:2–6
21. Beach MC, Morrison RS: The effect of do-not-resuscitate orders on physician decision-making. *J Am Geriatr Soc* 2002; 50:2057–2061
22. Chen JL, Sosnov J, Lessard D, et al: Impact of do-not-resuscitation orders on quality of care performance measures in patients hospitalized with acute heart failure. *Am Heart J* 2008; 156:78–84
23. Kish Wallace S, Martin CG, Shaw AD, et al: Influence of an advance directive on the initiation of life support technology in critically ill cancer patients. *Crit Care Med* 2001; 29:2294–2298
24. Vanpee D, Swine C: Scale of levels of care versus DNR orders. *J Med Ethics* 2004; 30:351–352
25. Martin E, McDonald J: What is MOLST? *R I Med J (2013)* 2014; 97:44–46
26. Brugger C, Breschi LC, Hart EM, et al: The POLST paradigm and form: Facts and analysis. *Linacre Q* 2013; 80:103–138
27. Mirarchi FL, Costello E, Puller J, et al: TRIAD III: Nationwide assessment of living wills and do not resuscitate orders. *J Emerg Med* 2012; 42:511–520
28. Fromme EK, Zive D, Schmidt TA, et al: POLST registry do-not-resuscitate orders and other patient treatment preferences. *JAMA* 2012; 307:34–35
29. Sinuff T, Cook DJ, Rocker GM, et al; Level of Care Study Investigators & the Canadian Critical Care Trials Group: DNR directives are established early in mechanically ventilated intensive care unit patients. *Can J Anaesth* 2004; 51:1034–1041
30. Bar-Or D, Salottolo KM, Orlando A, et al: Association between a geriatric trauma resuscitation protocol using venous lactate measurements and early trauma surgeon involvement and mortality risk. *J Am Geriatr Soc* 2013; 61:1358–1364
31. Hartog CS, Peschel I, Schwarzkopf D, et al: Are written advance directives helpful to guide end-of-life therapy in the intensive care unit? A retrospective matched-cohort study. *J Crit Care* 2014; 29:128–133