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COVID-19: Important Updates and Developments
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“Do-not-resuscitate (DNR)” status determines mortality in patients with COVID-19

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Abstract We investigatd the influence of do-not-resuscitate (DNR) status on mortality of hospital inpatients who died of COVID-19. This is a retrospective, observational cohort study of all patients admitted to two New Jersey hospitals between March 15 and May 15, 2020, who had, or developed, COVID-19 (1270 patients). Of these, 640 patients died (570 [89.1%] with and 70 [10.9%] without a DNR order at the time of admission) and 630 survived (180 [28.6%] with and 450 [71.4%] without a DNR order when admitted). Among the 120 patients without COVID-19 who died during this interval, 110 (91.7%) had a DNR order when admitted. Deceased positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients were significantly more likely to have a DNR order on admission compared with recovered positive SARS-CoV-2 patients ($P < 0.05$), similar to those who tested negative for SARS-CoV-2. COVID-19 DNR patients had a higher mortality compared with COVID-19 non-DNR patients (log rank $P < 0.001$). DNR patients had a significantly increased hazard ratio of dying (HR 2.2 [1.5-3.2], $P < 0.001$) compared with non-DNR patients, a finding that remained significant in the multivariate model. The risk of death from COVID-19 was significantly influenced by the patients’ DNR status.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in 815,476 global deaths and 178,129 in the United States as of August 25, 2020.[1] Do-not-resuscitate (DNR) orders are designed to allow for withholding cardiopulmonary resuscitation (CPR) in the event of cardiac arrest.[2,3] DNR status is often linked to patients with severe illness, advanced age, poor disease prognosis, and deteriorating health status with impending death.[4] Data are lacking on survivability of inpatient cardiac arrest for COVID-19 patients.[5] Voices of extreme views calling for a universal DNR policy for COVID-19 patients have created wide public outrage.[6] Certifying COVID-19 as the cause of death has driven up the

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statistics of the pandemic and affected health care decisions in the United States and globally.[7] The primary objective of this study was to identify the clinical outcome for patients with a DNR order who had death certificates attributing death to COVID-19.

Methods

Data source

Data were collected from patients who were admitted between March 15, 2020, to May 15, 2020, to two hospitals affiliated with our institution, including all patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR and were either deceased or had recovered. In addition, data on all patients who tested negative for SARS-CoV-2 and died during the same period were collected for comparison. The database was de-identified and met the criteria of the Health and Insurance Portability and Accountability Act (HIPAA) for the protection of personal information. The study was exempted by our institutional review board due to de-identifiability of data.

Study sample

Data from 1270 cases of positive SARS-CoV-2 patients (including 640 deceased and 630 recovered patients) and 120 deceased patients negative for SARS-CoV-2 admitted between 3/15/20 and 5/15/20 were extracted. All DNR patients included in this study had an active DNR order at the time of hospital admission. Patients who received a DNR order at any stage during their time in the hospital after admission were excluded to eliminate any confounding variables. All deceased patients had a death certificate stating that COVID-19 was the primary cause of death. Patient demographic data were collected with respect to age, age group ($<$60 and $\geq$60 years), sex, reason for admission, COVID-19 clinical manifestations at the time of admission, and comorbidities. Comorbidity data were collected for metabolic disease (ie, diabetes mellitus, electrolyte abnormality, vitamin deficiency, or anemias); lung disease (ie, chronic obstructive pulmonary disease, restrictive lung disease, or asthma); cardiovascular disease (ie, congestive heart failure; coronary artery disease; or peripheral vascular disease); kidney disease (ie, acute kidney injury, or chronic kidney disease); liver disease (ie, cirrhosis, hepatitis B/C, or alcoholic hepatitis); neurologic disease (ie, dementia, or cerebrovascular accidents); immunologic disease (ie, immunodeficiency disorders or autoimmune disease); or active malignancy at the time of admission. The study also reported the total number of days from admission until death or discharge.

Data analysis

The primary exposure of interest was a positive SARS-CoV-2 test confirmed by RT-PCR between March 15, 2020, and May 15, 2020. All other deceased patients with negative SARS-CoV-2 tests were included during the same period. Covariates included for analysis were age, sex, comorbidities, DNR status, hospital length of stay, vital status, and COVID-19 clinical manifestations at the time of admission.

Positive SARS-CoV-2-specific survival was analyzed using IBM SPSS Statistics 22 (IBM, Armonk, NY). Descriptive statistics are presented for categorical variables as frequencies and for continuous variables as medians with interquartile ranges (IQRs). Pearson's χ^2 test was used to evaluate for significant differences in hospital admission by DNR status. Kaplan-Meier, univariate, and multivariate Cox regression analyses were performed to calculate the hazard ratios (HRs) of all of the factors. To identify whether recovery or death was an independent risk factor associated with the DNR status, univariable and multivariate logistical regression models were analyzed for all the variables. Risk factors were defined as statistically significant with HRs not including 1.00 in their 95% confidence interval (CI), which indicate an alpha of $<$0.05. To evaluate the relationship between DNR status and the type of comorbidity, we quantified each comorbidity in the cohort relative to the DNR status, and we calculated the HRs in univariate and multivariate Cox regression models to assess their influence on mortality for DNR patients.

Results

Patient characteristics

A total of 1380 patients with confirmed SARS-CoV-2 tests were identified: median age, 66.44 years (interquartile range, 52.6-76.3 years). Of these 1380 patients, 630 recovered with positive SARS-CoV-2, including 180 (28.6%) with DNR and 450 (71.4%) non-DNR, and 640 died with death certificates attributing COVID-19 as the cause of death, including 570 (89.1%) with DNR and 70 (10.9%) non-DNR. During the study period, there were 120 deceased patients with negative SARS-CoV-2 testing, including 110 (91.7%) with DNR and 10 (8.3%) non-DNR (Figure 1). Descriptive statistics are presented in Table 1. DNR patients were significantly older (76.3 vs 66.4 years) than non-DNR patients. Men were significantly more frequent than women overall in this cohort, and men with DNR were significantly more numerous than men with non-DNR status. Older patients ($\geq$60 years) had significantly higher DNR rates than younger patients ($<$60 years). Recovered patients with positive SARS-CoV-2 had significantly higher non-DNR status compared with the DNR counterpart, and vice versa in those who died. There was no statistical significance in terms of presenting with COVID-19 clinical manifestations between DNR and non-DNR patients; however, DNR patients were more likely to present

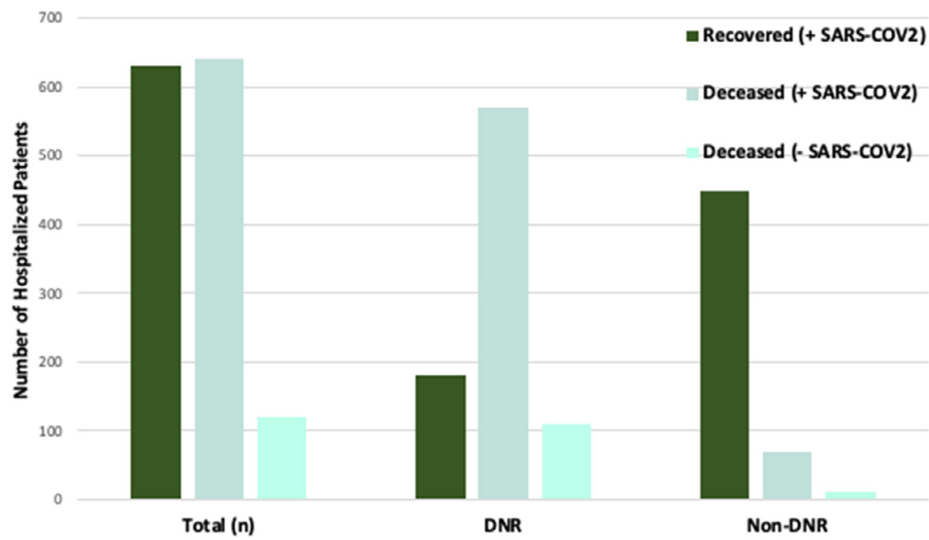

Figure 1 Comparison of the three study groups of the cohort, showing a significantly higher percentage of deceased COVID-19 patients with do-not-resuscitate (DNR) order on admission compared with a significantly higher percentage of recovered patients with SARS-COV negative test or non-DNR on admission.

Table 1 Descriptive statistics of the cohort.

Group	DNR (%)	No-DNR (%)	Total	χ^2
Sex				
M	790 (62.7)	470 (37.3)	1260	**<0.05***
F	70 (53.8)	60 (46.2)	130	>0.05
Age (y)				
<60	140 (45.2)	170 (54.8)	310	**<0.05***
≥60	720 (66.67)	360 (33.33)	1080	**<0.05***
SARS-CoV-2				
Positive	750 (59.1)	520 (40.9)	1270	**<0.05***
Negative	110 (91.67)	10 (8.3)	120	**<0.05***
Group				
Recovered (+ SARS-CoV-2)	180 (12.9)	450 (32.4)	630	**<0.05***
Deceased (+ SARS-CoV-2)	570 (41)	70 (5)	640	**<0.05***
Deceased (− SARS-CoV-2)	110 (7.9)	10 (0.8)	120	**<0.05***
COVID-19 clinical manifestations at admission				
Yes	380 (52.78)	340 (47.2)	720	>0.05
No	480 (71.64)	190 (28.36)	670	**<0.05***
Comorbidities				
0	0 (0)	10 (100)	10	>0.05
1	30 (30)	70 (70)	100	**<0.05***
2	280 (57.1)	210 (42.9)	490	>0.05
3	380 (69.1)	170 (30.9)	550	**<0.05***
4	130 (76.5)	40 (23.5)	170	**<0.05***
5	30 (50)	30 (50)	60	>0.05
6	10 (100)	0 (0)	10	>0.05
Average length of hospital stay (days)	17.38 ± 2.66	9.6 ± 1.55		**<0.05***

DNR, do-not-resuscitate.
* $P < 0.05$ is considered significant (in bold).

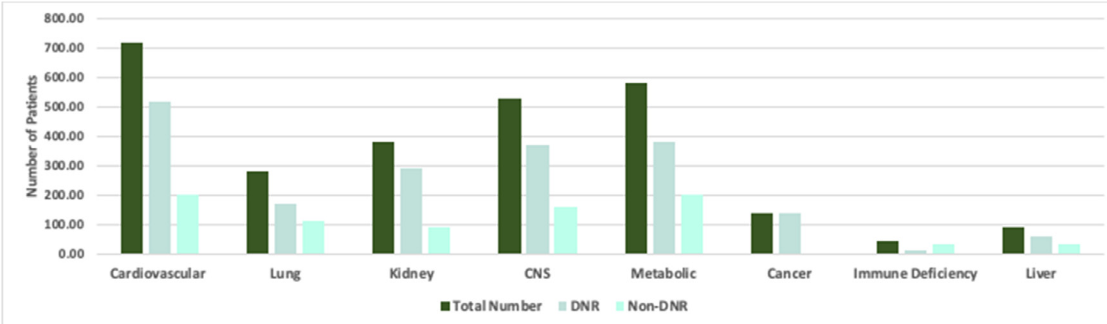

Figure 2 Quantification of each comorbidity in the cohort relative to the do-not-resuscitate status.

Table 2 Cox regression analysis showing the hazard ratios in the univariate and multivariate models for each comorbidity in COVID-19 patients.

Comorbidity	Univariate			Multivariate		
	HR*	95% CI	*P*	HR*	95% CI	*P*
Cardiovascular	1.95	1.81-2.2	0.6	1.88	1.7-2.1	0.2
Lung	1.2	1.1-1.3	**0.002**†	1.2	1.1-1.3	**0.001**†
Kidney	1.01	0.95-1.1	**0.6**	1.94	1.87-2.1	0.1
CNS	21.83	1.77-1.89	**0.0001**†	1.79	1.73-1.86	**0.0001**†
Metabolic	1.9	1.85-1.98	**0.02**†	1.96	1.89-2.1	0.3
Cancer	1.76	1.7-1.8	**0.0001**†	1.71	1.65-1.77	**0.0001**†
Immune Deficiency	1.6	1.2-2.23	**0.002**†	1.5	1.1-2.1	**0.01**†
Liver	1.87	1.7-2.1	0.1	1.83	1.7-2.1	0.1

DNR, do-not-resuscitate; HR, hazard ratio.

* HR >1 in Cox regression is interpreted as an increase in the hazard of dying from COVID-19 in DNR patients compared with non-DNR patients. Baseline reference: No cardiovascular diseases, no lung diseases, no kidney diseases, no CNS diseases, no metabolic diseases, no cancer, no immune deficiency diseases, no liver diseases.

† $P < 0.05$ is considered significant (in bold).

with a nonrelated (to COVID-19) chief complaint. Patients with DNR had significantly higher numbers of comorbidities (>3 comorbidities) compared with patients with non-DNR status; however, there was no statistical significance between the two groups when comparing the average number of overall comorbidities. Further analyses revealed that, as expected, comorbidities emerged to be higher in DNR than non-DNR patients with cardiovascular diseases displaying the greater difference between the two groups (Figure 2). All comorbidities increased the hazard of dying with variable significance Table 2. Lung, central nervous system (CNS), metabolic, cancer, and immune deficiency diseases increased the hazard significantly in the univariable model. Lung, CNS, cancer, and immune deficiency diseases remained significant in the multivariable model. Interestingly, although cardiovascular diseases were significantly higher in DNR patients, this did not associate with a poorer prognosis. Also, kidney and liver diseases increased the hazard of dying but not significantly on both the univariable and multivariable models.

The average length of hospital stay (days) were almost twice as high in those with DNR compared with those with non-DNR status (17.36 ± 2.66 vs 9.58 ± 1.55 days, $P = 0.01$).

Association of DNR status with survival

A Kaplan-Meier plot shows that survival was influenced by DNR status in all positive SARS-CoV-2 patients (Figure 3A). Patients with DNR had a poorer survival rate than non-DNR patients (log rank P value <0.05). The mean survival time in DNR patients was 11.6 ± 1.3 days (95% CI, 9-14.2) compared with non-DNR patients (28.5 ± 3 days [95% CI, 22.7-34.3]), log-rank test, $P < 0.001$). When comparing the survival based on sex, there was no statistical difference between DNR and non-DNR groups ($P > 0.05$; Figure 3B). Although there was no statistical significance in survival between younger (<60 years) and older (≥60 years) age groups of DNR patients (Figure 3C), younger patients (<60 years) had a significantly better survival rate compared with older patients (≥60 years) in the non-DNR group: log-rank test, $P = 0.04$; HR = 1.8 (95% CI, 1.6-2.7) (Figure 3D).

In univariate Cox regression, DNR patients had a higher HR for risk of death (HR) than non-DNR patients (HR, 2.2;

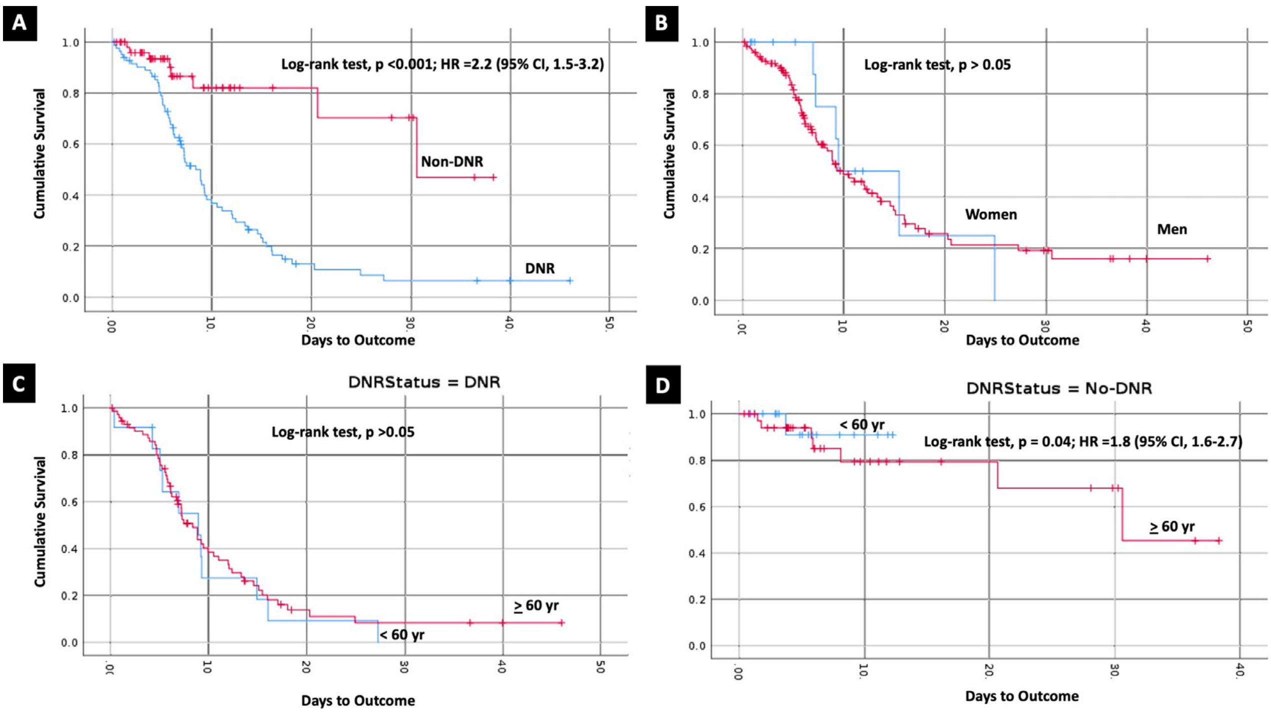

Figure 3 Kaplan-Meier plots showing a comparative cumulative survival of do-not-resuscitate (DNR) versus non-DNR patients with COVID-19 **(A)**, men versus women, **(B)**, and patients <60 versus ≥60 years of age with DNR **(C)** and with non-DNR **(D)**. Log-rank *P* values were calculated to evaluate significance ($P < 0.05$ is considered significant).

Table 3 Cox regression analysis showing the hazard ratios in the univariate and multivariate models for the different variables in COVID-19 patients.

Variable	Univariate			Multivariate		
	HR*	95% CI	*P*	HR*	95% CI	*P*
Sex	0.9	0.4-2	>0.05	0.8	0.3-1.9	>0.05
Age (y)	1	0.7-1.4	>0.05	1	0.99-1.1	>0.05
SARS-CoV-2	1.5	1.1-2.1	**<0.05**†	2.5	0.9-2.8	>0.05
DNR status	2.2	1.5-3.2	**<0.001**†	2.2	1.4-3.5	**<0.001**†
COVID-19 clinical manifestations on admission	1	0.8-1.2	>0.05	1	0.7-1.3	>0.05
Comorbidities	1.2	0.9-1.5	>0.05	1.1	0.8-1.4	>0.05

DNR, do-not-resuscitate; HR, hazard ratio.
* HR >1 in Cox regression is interpreted as an increase in the hazard of dying from COVID-19 in DNR patients compared with non-DNR patients.
† $P < 0.05$ is considered significant (in bold).

95% CI, 1.5-3.2) ($P < 0.001$) (Table 3), and when adjusting for other variables in the multivariable model, DNR patients remained with a higher HR than non-DNR patients (HR, 2.2; 95% CI, 1.4-3.5; $P < 0.001$) (Table 3). SARS-CoV-2 test positivity was associated with increased HRs compared with a negative test in the univariate model (HR, 1.5; 95% CI, 1.1-2.1; $P < 0.05$); however, these results did not remain significant in the multivariable model; moreover, when comparing multiple variables (ie, age, sex, COVID-19 clinical manifestations on admission, and the number of comorbidities) with univariate and multivariate Cox regression, there was no statistical significance between the HRs.

Discussion

The significance of DNR status as an independent risk factor for mortality has not been documented previously in COVID-19 patients. The present study analyzed data of 1270 patients with COVID-19, who were admitted to our institutions during the peak of the COVID-19 pandemic in New Jersey. DNR patients had higher HRs for risk of death and lower survival outcomes compared with non-DNR patients. The association between DNR status and poor clinical outcomes remained independently significant after adjustment for important clinical factors, including age, sex, COVID-

19 clinical manifestations at the time of admission, and comorbidities.

One explanation for these results is that more patients with a DNR order died because they were not resuscitated.[8] Another hypothesis is that in the face of rapid clinical deterioration, DNR patients may be more likely to be placed on comfort care (hospice) compared with non-DNR patients [4]; however, due to the retrospective study design, reasons for a DNR order cannot be determined.

Overall, DNR patients were older and had more comorbidities. This suggests that the DNR order may be a proxy for more severe illness. The comorbidity clusters were different from one patient to another, and there was not enough data for each cluster to derive a meaningful conclusion. The severity of each comorbidity was not easy to measure due to the retrospective nature of the study. Some but not all patients had a record of cardiac ejection fraction percent noted and some but not all had the degree of chronic kidney disease noted. Our further analyses revealed that DNR patients had more comorbidities than non-DNR patients and that the type of comorbidities increased the hazard of dying in the DNR group, which support the concept of considering DNR as a surrogate for prognosis. Notably, a DNR order has been documented to negatively impact the implementation of other treatment modalities (ie, "failure to rescue phenomenon"),[4] which could explain the increased mortality of these patients.

SARS-CoV-2 positivity and older age had a negative impact on survival. These findings have been previously reported [9]; however, those factors did not remain significant when adjusting for other variables in the multivariable model, which further support the importance of considering DNR status when analyzing mortality of COVID-19 patients.

DNR status may be requested by patients and/or their families to avoid prolonged life support, including application of a respirator, at the end of life when there is little or no expectation that this will be followed by a more normal existence. Treatment for severe COVID-19 may require such measures as well, but usually for only a much shorter interval, days or weeks, and usually with a good expectation of a normal or near-normal existence on recovery. Patients with severe COVID-19 whose physicians feel that they need such measures short-term to treat the disease may be discouraged from offering them if the patient has a DNR order. This may unnecessarily negatively impact patient care and increase mortality in COVID-19 patients. Our findings agree with the stated opinions of Curtis and Mirarchi, who in their editorial about the importance of clarity for hospital code status orders note that DNR documentation is interpreted more broadly than may have been the patient's intention.[10]

Finally, the average length of the hospital stay (days) was almost twice as high in those with DNR status compared with those with non-DNR status. Recovered patients were mostly non-DNR patients in this cohort, which could support that resuscitation in the event of respiratory failure caused by COVID-19 was the reason for a shorter inpatient stay; however, there was no clear record in the analyzed data on the resuscitation protocols used during inpatient time to evaluate this hypothesis.

Limitations

The limitations of this study include the retrospective nature. Misclassification of data is possibly attributable to inaccurate coding; however, there is no reason to suspect that this would occur in any particular direction for the DNR status, because misclassification would likely be nondifferential in nature and likely biased toward the null. It may be appropriate to perform one or more prospective studies to further examine these issues.

Conclusions

In this cohort of patients with COVID-19, a DNR order was found to be a significant predictor of mortality, a finding that persisted after adjustment for other important clinical factors. The increased mortality in DNR patients may have resulted from unmeasured severity of illness, transition to comfort care in accordance with a patient's wishes, or failure to offer more aggressive care, such as a respirator, to patients with a DNR order. DNR status should be evaluated in COVID-19 epidemiologic studies to further understand mortality in this pandemic.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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