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Patient and Hospital-Level Characteristics Associated with the Use of Do-Not-Resuscitate Orders in Patients Hospitalized for Sepsis

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BACKGROUND: Identifying factors associated with do-not-resuscitate (DNR) orders is an informative step in developing strategies to improve their use. As such, a descriptive analysis of the factors associated with the use of DNR orders in the early and late phases of hospitalizations for sepsis was performed.

METHODS: A retrospective cohort of adult patients hospitalized for sepsis was identified using a statewide administrative database. DNR orders placed within 24 h of hospitalization (early DNR) and after 24 h of hospitalization (late DNR) were the primary outcome variables. Multivariable logistic regression analysis was used to identify patient, hospital, and healthcare system-related factors associated with the use of early and late DNR orders.

RESULTS: Among 77,329 patients hospitalized for sepsis, 27.5 % had a DNR order during their hospitalization. Among the cases with a DNR order, 75.5 % had the order within 24 h of hospitalization. Smaller hospital size and the absence of a teaching program increased the likelihood of an early DNR order being written. Additionally, greater patient age, female gender, White race, more medical comorbidities, Medicare payer status and admission from a skilled nursing facility were all significantly associated with the likelihood of having an early DNR. The strength of association between these factors and the use of late DNR orders was weaker. In contrast, the greater the burden of medical comorbidities, the more likely a patient was to receive a late DNR order.

CONCLUSION: Multiple patient, hospital, and healthcare system-related factors are associated with the use of DNR orders in sepsis, many of which appear to be independent of a patient's clinical status. Over the course of the hospitalization, the burden of medical illness shows a stronger association relative to other variables. The influence of these multi-level factors needs to be recognized in strategies to improve the use of DNR orders. .

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INTRODUCTION

Sepsis, defined as a systemic inflammatory response due to infection, is a leading cause of morbidity and mortality in critically ill patients. There are approximately 750,000 cases of sepsis per year in the United States.[1] In addition, the most extreme clinical manifestations of sepsis, severe sepsis and septic shock have mortality rates of 25 to 50 %.[1–3] As a result, end-of-life issues are a common and important part of sepsis clinical management.[4] Because advanced medical interventions have the capability to maintain survival in health states perceived to be undesirable, an important element of end-of-life care is the use of do-not-resuscitate (DNR) orders. In patients whose prognoses are so poor that they are not expected to derive benefit from cardiopulmonary resuscitation, or in patients whose values and preferences are against aggressive resuscitation, DNR order sallow caretakers to potentially reduce patient suffering, comply with patient wishes, and rationalize the delivery of healthcare.[5] As such, understanding the factors that influence DNR orders and making their implementation more effective has the potential to improve the care of critically-ill patients with sepsis.

Previous studies in mixed medical populations suggest that for a given medical condition, medical comorbidities, severity of illness, as well as sociodemographic, institutional and geographic factors contribute to the propensity of having a DNR order.[6–9] Because administrative data typically captures only those DNR orders placed in the first 24 h of hospitalization, most studies have only examined factors that are associated with early DNR orders. However, the factors that influence the likelihood of a DNR order later in the hospital course may be different. A recent change in the DNR reporting requirement for the California Office of Statewide Health Planning and Development (OSHPD) differentiates between DNR orders placed less than 24 h into a hospitalization (early DNR) and those made after 24 h (late DNR). This change created an opportunity to examine the use of DNR orders longitudinally over the course of a hospitalization. As such, the purpose of this study was to examine the patient, hospital, and healthcare systems factors associated with the presence of a DNR order in the early and late phases of hospitalization in patients admitted with sepsis. We chose to focus our analysis on patients admitted with sepsis because the use of DNR orders is highly relevant in this population and doing so would minimize the heterogeneity associated with examining DNR use across multiple different medical conditions.

MATERIALS AND METHODS

Data

The data for this study was obtained from the California Office of Statewide Health Planning and Development (OSHPD) patient discharge database public file for the year 2011.[10] In California, discharge abstracts from all patients who were hospitalized in a California-licensed hospital are compiled into a publicly available data set. The data set includes de-identified information on patient race / ethnicity, age, gender, insurance type, ZIP code of residence, primary and secondary diagnosis and procedure codes, level of care, source of admission, DNR order (first 24 h of hospitalization and after 24 h of hospitalization), and hospital identification code. Hospital characteristics, including size (number of beds) and teaching status, were obtained separately from the California OSHPD hospital financial and utilization reports for 2011.[11]

Study Design

This was a retrospective cohort study of adult patients (age/ ;18) in the OSHPD database who were hospitalized for sepsis in California during 2011. Hospitalizations for sepsis were identified based on the presence of a compatible International Classification of Diseases, ninth revision, Clinical Modification (ICD-9 CM) code as the principal diagnosis for hospital admission. The ICD-9 CM codes that were used for sepsis were: 038.XX (septicemia), 020.0 (septicemic), 790.7 (bacteremia), 117.9 (disseminated fungal infection), 112.5 (disseminated candida infection), and 112.81 (disseminated fungal endocarditis). These ICD-9 CM codes have previously been used in population-based studies of sepsis.[1,2,12,13] Additional details regarding the use of these codes are included in the Supplementary Online Appendix. In order to protect patient confidentiality, records with unique combinations of key demographic variables are masked in the OSHPD public database. The order in which the variables were masked in the OSHPD data set are: 1) age, 2) ethnicity and race, 3) sex, 4) admission quarter, and 5) patient ZIP code. For our study, records with masked variables or missing data were excluded so that a complete case analysis of all relevant variables could be performed. Patients were also excluded from the analysis if they were hospitalized at a non-acute care facility (rehabilitation, psychiatric, drug and alcohol dependency center) or were younger than 18 years of age. The study was approved as an exempt protocol by the institutional review board at the Los Angeles Biomedical Research Institute.

Statistical Analysis

The primary outcome variables were the presence of a DNR order in the first 24 h (early DNR) and after 24 h (late DNR) of hospitalization. The independent variables included hospital-associated factors (number of beds, teaching status), patient factors (age, ethnicity / race, gender, comorbid conditions), and healthcare systems related factors (payment status, health maintenance organization [HMO] insurance, and source of admission). Comorbid conditions were identified using discharge data codes to calculate a Charlson Comorbidity Index.[14–16] In order to examine the relationship between the independent variables and DNR use, we generated multivariable logistic regression models using early DNR compared to no DNR and late DNR compared to no DNR as the dependent variables.

As this was a descriptive analysis intended to examine the relationship of each of these independent variables to the primary outcomes, all independent variables were included in the final models. The performance of the models was assessed by the c-statistic, calculated as the area under the Receiver Operating Characteristic (ROC) curve based on fitted probabilities from the model and the true values. The odds ratio of having a DNR order based on each independent variable was determined from the regression coefficients in the logistic regression models. The statistical significance of the regression coefficients was examined using the Wald statistic ($p<0.05$ for statistical significance). The data are presented as adjusted odds ratios with 95 % confidence intervals (CI). Adjusted odds ratios with a 95 % CI excluding 1.00 were considered statistically significant. The data analysis was performed using JMP version 11.0 (SAS Institute, Cary, NC).

As we were using a large administrative database with the potential for bias, we chose to validate our findings by examining the prevalence of DNR orders in patients in the OSHPD database who were admitted with a cerebrovascular accident (CVA). Admissions for CVA were chosen because the use of DNR orders has been extensively studied in this population. As such, the prevalence of DNR orders in other studies using different methodologies was available for comparison with our data.[8,17] The ICD-9 CM codes used in our study to identify patients admitted with a CVA were 430.XX–434.XX, 436.XX, and 437.XX. Additional information regarding the CVA cohort is included in the Supplementary Online Appendix.

RESULTS

A total of 141,000 hospitalizations for sepsis were identified from the OSHPD patient discharge database in 2011 (Fig. 1). Of these, 63,671 cases (45.2 %) were excluded. A total of 61,230 exclusions (96.2 %) were due to masking of one or more variables in the OSHPD database for de-identification. Reasons for exclusions are shown in Figure 1. A total of 77,329 hospitalizations were available for analysis after exclusions. Of these, 21,290 cases (27.5 %) had a DNR order during the hospitalization. Among the cases with a DNR order, 16,071 (75.5 %) had a DNR within the first 24 h of admission and 5,219 (24.5 %) had a DNR after 24 h. The baseline characteristics of the study cohort are shown in Table 1. Nearly 80 % of patients admitted for sepsis were older than 60 years, and 42 % of patients were 80 years or older. Non-Hispanic, White patients comprised 57 % of the study population. Approximately 18 % of cases were from patients of Hispanic ethnicity. Black and Asian patients each comprised 8 % of the cases. Most patients in the cohort were admitted to the hospital from home. Although the most prevalent payer category was Medicare (73 %), 24 % of patients had either Medi-Cal or indigent payer status. Most patients had multiple comorbidities as defined by the Charlson Comorbidity Index. The distribution of some common comorbid conditions is shown in Table 1. Most patients with sepsis were admitted at non-teaching hospitals. The hospital mortality of the overall population was 14.7 %. The mortality was higher in the patients who had early and late DNR orders compared to those who did not have a DNR order.

Multivariable logistic regression analysis was used to examine the factors that were associated with the odds of having a DNR order during a hospitalization for sepsis (Tables 2 and 3). Overall, teaching status of the hospital, patient age, payment category, and the Charlson Comorbidity Index showed the greatest quantitative differences between bivariate and multivariable analyses. Multiple institutional, patient-related, and healthcare-associated factors influenced the likelihood of having a DNR order in the first 24 h of hospitalization (Table 2). Associated institutional factors included hospital size (OR 1.31, 95 % CI 1.18–1.46, between smallest and largest hospital) and teaching status (OR 1.18, 95 % CI 1.10–1.27, teaching vs. non-teaching). Associated patient-related factors included age, gender, race / ethnicity, and medical comorbidities. Notably, there was a significant decrease in the odds of having a DNR order among all non-White racial / ethnic groups. The largest difference was seen between Black and White patients, as Black patients with sepsis were less than half as likely to receive a DNR order. Hispanic and Asian patients were approximately 40 % less likely to have a DNR order than White patients. Finally, healthcare-associated factors such as payer category and source of admission were also significantly associated with the likelihood of having a DNR. Compared to the Medicare group, patients who were indigent (OR 0.34, 95 % CI 0.20–0.53) or who had Medi-Cal (OR 0.69, 95 % CI 0.63–0.75) had significantly decreased odds of having a DNR order. The c-statistic was 0.75 for the early DNR model.

A separate multivariable logistic regression model was used to examine the association of these variables on the

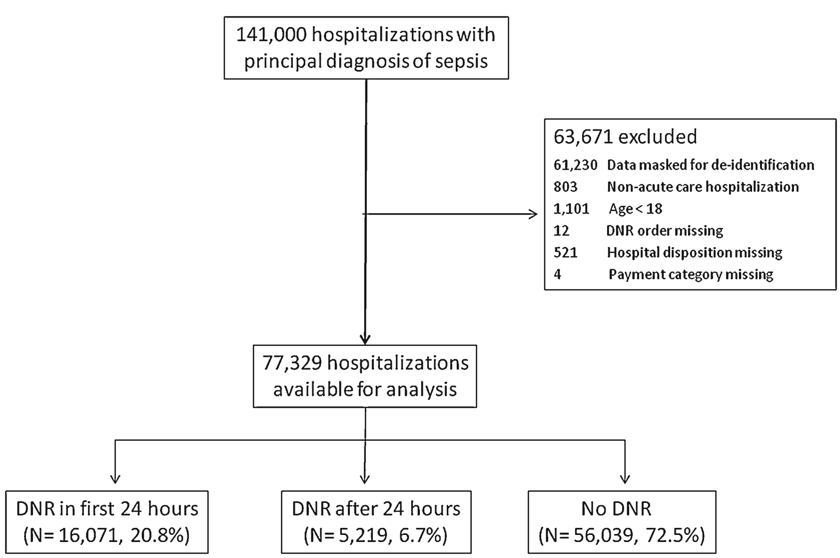

Figure 1. Hospitalizations for sepsis included in the data analysis and the distribution of do-not-resuscitate (DNR) orders.

Table 1. Baseline Characteristics

Characteristic	Overall (N=77,329)	DNR first 24 h (N=16,071)	DNR after 24 h (N=5,219)	No DNR (N=56,039)
Hospital size, no. beds				
1–99	4,367 (5.6)	996 (6.2)	302 (5.8)	3,069 (5.5)
100–199	15,856 (20.5)	3,273 (20.4)	993 (19.0)	11,590 (20.7)
200–499	49,473 (64.0)	10,502 (65.4)	3,430 (65.7)	35,541 (63.4)
500+	7,633 (9.9)	1,300 (8.1)	494 (9.5)	5,839 (10.4)
Teaching hospital	8,724 (11.3)	1,476 (9.2)	502 (9.6)	6,746 (12.0)
Age				
80+	32,261 (41.7)	11,043 (68.7)	3,113 (59.6)	18,105 (32.3)
70–79	15,522 (20.1)	2,649 (16.5)	993 (19.0)	11,880 (21.2)
60–69	12,568 (16.3)	1,344 (8.4)	601 (11.5)	10,623 (19.0)
50–59	9,084 (11.7)	733 (4.6)	335 (6.4)	8,016 (14.3)
18–49	7,894 (10.2)	302 (1.9)	177 (3.4)	7,415 (13.2)
Female gender	41,887 (54.2)	9,406 (58.5)	2,896 (55.5)	29,585 (52.8)
Race / ethnicity				
White	43,768 (56.6)	11,604 (72.2)	3,316 (63.5)	28,904 (51.6)
Black	6,286 (8.1)	696 (4.3)	344 (6.6)	5,246 (9.4)
Hispanic	13,919 (18.0)	1,657 (10.3)	710 (13.6)	11,561 (20.6)
Asian	6,324 (8.1)	1,184 (7.4)	502 (9.6)	4,638 (8.3)
Other	7,032 (9.1)	930 (5.8)	347 (6.7)	5,690 (10.1)
Source of admission				
Home	58,573 (75.7)	10,273 (63.9)	3,633 (69.6)	44,667 (79.7)
Skilled nursing and assisted living	15,285 (19.8)	5,097 (31.7)	1,388 (26.6)	8,800 (15.7)
Acute care hospital	2,150 (2.8)	359 (2.2)	129 (2.5)	1,662 (3.0)
Other	1,321 (1.7)	342 (2.1)	69 (1.3)	910 (1.6)
Payment category				
Medicare	56,130 (72.6)	14,167 (88.2)	4,304 (82.5)	37,659 (67.2)
Indigent	8,842 (11.4)	685 (4.3)	15 (0.3)	766 (1.4)
Medi-Cal	9,452 (12.2)	1,062 (6.6)	411 (7.9)	7,746 (13.8)
Private	799 (1.0)	18 (0.1)	399 (7.6)	7,991 (1.4)
Self-pay	1,424 (1.9)	67 (0.4)	49 (0.9)	1,308 (2.3)
Other	682 (0.9)	72 (0.4)	41 (0.7)	569 (1.0)
HMO insurance plan	28,072 (36.3)	6,488 (40.4)	1,595 (30.6)	19,989 (35.6)
Charlson Comorbidity Index				
0	8,295 (10.7)	958 (6.0)	266 (5.1)	7,071 (12.6)
1–3	32,243 (41.7)	7,115 (44.3)	2,144 (41.1)	22,984 (41.0)
4–6	27,773 (35.9)	5,819 (36.2)	1,924 (36.9)	20,030 (35.7)
7–9	6,549 (8.5)	1,483 (9.2)	577 (11.1)	4,489 (8.0)
10+	2,469 (3.2)	696 (4.3)	308 (5.9)	1,465 (2.6)
Comorbid conditions				
Congestive heart failure	55,949 (27.6)	5,304 (33.0)	1,672 (32.0)	14,404 (25.7)
Dementia	18,086 (23.4)	6,366 (39.6)	1,857 (35.6)	9,863 (17.6)
Cerebrovascular disease	1,230 (1.6)	363 (2.3)	97 (1.9)	770 (1.4)
Chronic obstructive pulmonary disease	14,722 (14.7)	2,169 (13.5)	703 (13.5)	8,512 (15.2)
Diabetes mellitus	28,722 (37.2)	4,960 (30.9)	1,600 (30.7)	22,212 (39.6)
Malignancy	12,971 (16.7)	3,251 (20.2)	1,396 (26.7)	8,324 (14.9)
Mortality	11,374 (14.7)	4,659 (29.0)	2,079 (39.8)	4,636 (8.3)
Length of stay (median days, interquartile range [IQR])	5.0 (6.0)	4.0 (5.0)	6.0 (7.0)	6.0 (7.0)

odds of having a DNR after 24 h of hospitalization (Table 3). Unlike early DNR use, hospital-related factors (hospital size and teaching status) were not associated with the odds of having a late DNR. Compared to the early DNR model, the odds ratios for age, race / ethnicity, source of admission, and payer category and having a late DNR order were smaller, although still statistically significant. On the other hand, the odds ratios of having a late DNR order were higher within each category of the Charlson Comorbidity index compared to early DNR. The c-statistic was 0.71 for the late DNR model.

In order to understand the potential impact of the excluded cases on the associations identified in our study, we analyzed the hospitalizations that were excluded due to data masking and de-identification (Supplementary Figure 1 and Supplementary Tables 1–3). The distribution of missing data due to masking was 100 % for age, 61.3 % for ethnicity and race, and 33.4 % for sex (Supplementary Figure 1). Although there were some differences between the primary study cohort and excluded cohort in payment category and the frequency of DNR orders in the first 24 h, the overall distribution of the other baseline characteristics was similar (Supplementary Table 1). Multivariable logistic regression models of early and late DNR use in the excluded cohort and primary study cohort showed that the adjusted odds ratios of the independent variables, with the exception of small hospital size on early DNR, were similar (Supplementary Tables 2 and 3).

In order to help validate our approach to using the OSHPD data set and the findings in the sepsis cohort, we examined the prevalence of DNR orders in patients admitted with a CVA using ICD-9 CM codes that were previously described in the medical literature.[17] A total of 34,799 admissions for CVA were identified. Of those, a DNR

Table 2. Factors Associated with Early DNR Use in Patients with Sepsis

Variable	Bivariate analysis		Multivariable analysis	
	OR	95 % CI	Adj OR	95 % CI
Hospital size, no. beds				
1–99	1.44	(1.31, 1.58)	1.31	(1.18, 1.46)
100–199	1.27	(1.18, 1.36)	1.07	(0.99, 1.18)
200–499	1.31	(1.23, 1.40)	1.09	(1.01, 1.18)
500+	1.00		1.00	
Teaching hospital	0.75	(0.71, 0.80)	1.18	(1.10, 1.27)
Age				
80+	13.08	(11.66, 14.74)	7.36	(6.49, 8.37)
70–79	5.17	(4.59, 5.86)	2.97	(2.61, 3.39)
60–69	3.01	(2.65, 3.43)	1.95	(1.71, 2.24)
50–59	2.21	(1.92, 2.54)	1.72	(1.50, 1.98)
18–49	1.00		1.00	
Female gender	1.25	(1.21, 1.30)	1.16	(1.12, 1.21)
Race / ethnicity				
White	1.00		1.00	
Black	0.42	(0.38, 0.45)	0.42	(0.39, 0.46)
Hispanic	0.46	(0.43, 0.48)	0.59	(0.55, 0.63)
Asian	0.77	(0.72, 0.82)	0.61	(0.57, 0.65)
Other	0.51	(0.48, 0.55)	0.88	(0.80, 0.96)
Source of admission				
Home	1.00		1.00	
Skilled nursing and assisted living	2.35	(2.26, 2.45)	2.04	(1.96, 2.13)
Acute care hospital	0.94	(0.84, 1.06)	0.88	(0.78, 0.99)
Other	1.64	(1.45, 1.86)	1.51	(1.31, 1.73)
Payment category				
Medicare	1.00		1.00	
Indigent	0.07	(0.04, 0.11)	0.34	(0.20, 0.53)
Medi-Cal	0.24	(0.23, 0.27)	0.69	(0.63, 0.75)
Private	0.37	(0.35, 0.40)	0.68	(0.63, 0.74)
Self-pay	0.14	(0.11, 0.19)	0.61	(0.47, 0.78)
Other	0.35	(0.27, 0.44)	0.86	(0.66, 1.10)
HMO insurance plan	1.24	(1.20, 1.29)	1.58	(1.52, 1.65)
Charlson Comorbidity Index				
0	1.00		1.00	
1–3	2.17	(2.02, 2.33)	1.42	(1.32, 1.54)
4–6	2.03	(1.89, 2.19)	1.44	(1.33, 1.56)
7–9	2.24	(2.05, 2.45)	1.95	(1.77, 2.14)
10+	3.01	(2.69, 3.36)	3.12	(2.77, 3.52)

Table 3. Factors Associated with Late DNR Use in Patients with Sepsis

Variable	Bivariate analysis		Multivariable analysis	
	OR	95 % CI	OR	95 % CI
Hospital size, no. beds				
1–99	1.07	(0.92, 1.24)	1.01	(0.86, 1.18)
100–199	0.97	(0.86, 1.08)	0.88	(0.78, 1.00)
200–499	1.08	(0.98, 1.19)	1.01	(0.90, 1.13)
500+	1.00		1.00	
Teaching hospital	0.83	(0.75, 0.91)	0.97	(0.88, 1.09)
Age				
80+	4.66	(4.01, 5.45)	3.75	(3.17, 4.45)
70–79	2.98	(2.54, 3.52)	2.38	(2.00, 2.85)
60–69	2.19	(1.85, 2.60)	1.77	(1.48, 2.11)
50–59	1.67	(1.39, 2.01)	1.40	(1.17, 1.70)
18–49	1.00		1.00	
Female gender	1.06	(1.00, 1.12)	1.02	(0.96, 1.08)
Race / ethnicity				
White	1.00		1.00	
Black	0.77	(0.69, 0.86)	0.80	(0.71, 0.90)
Hispanic	0.70	(0.65, 0.76)	0.85	(0.77, 0.94)
Asian	1.15	(1.04, 1.27)	0.94	(0.85, 1.04)
Other	0.69	(0.62, 0.78)	0.85	(0.74, 0.96)
Source of admission				
Home	1.00		1.00	
Skilled nursing and assisted living	1.51	(1.42, 1.61)	1.26	(1.17, 1.34)
Acute care hospital	0.96	(0.80, 1.15)	0.94	(0.77, 1.12)
Other	0.83	(0.65, 1.06)	0.85	(0.66, 1.08)
Payment category				
Medicare	1.00		1.00	
Indigent	0.23	(0.13, 0.37)	0.61	(0.35, 0.99)
Medi-Cal	0.59	(0.53, 0.65)	1.09	(0.97, 1.23)
Private	0.53	(0.48, 0.59)	1.05	(0.93, 1.19)
Self-pay	0.43	(0.32, 0.56)	0.99	(0.73, 1.32)
Other	0.77	(0.55, 1.04)	1.32	(0.94, 1.81)
HMO insurance plan	0.76	(0.71, 0.81)	0.81	(0.75, 0.86)
Charlson Comorbidity Index				
0	1.00		1.00	
1–3	2.15	(1.89, 2.45)	1.63	(1.43, 1.86)
4–6	2.25	(1.98, 2.57)	1.76	(1.54, 2.02)
7–9	2.92	(2.52, 3.39)	2.54	(2.18, 2.95)
10+	4.30	(3.63, 5.11)	3.97	(3.33, 4.73)

order was placed during the hospitalization in 6,688 cases (19.2 %). Shepardson et al. showed that DNR orders were written in 22 % of admissions for a CVA in an urban, multi-center cohort of 13,337 patients.[17] Wenger et al. showed that a DNR order was present in 21 % of admissions admitted with a CVA in a large sample of Medicare patients.[8] Thus, the prevalence of DNR orders identified in the OSHPD cohort using our methodologic approach was comparable to previous studies. The baseline characteristics of the CVA population in the OSHPD database and multivariable analyses on the factors associated with early and late DNR use are shown in Supplementary Tables 4–6.

DISCUSSION

This evaluation of a diverse statewide patient population using a large administrative database showed that DNR orders were written in greater than 25 % of patients hospitalized for sepsis. Of those, approximately 75 % of patients had DNR orders within 24 h of admission to the hospital. These findings show that the use of a DNR order is common in patients admitted with sepsis, and the DNR order frequently reflects decisions made before hospitalization or very early in the hospital course. To our knowledge, only one previous study has examined the prevalence of DNR orders in sepsis.[18] In that study, patients were retrospectively identified using a clinical definition of sepsis at a single academic institution. Within the cohort, 13 % of patients had DNR orders during their hospitalization. In our study, we used a case definition of sepsis based on diagnosis codes from an administrative database. While data using administrative diagnosis codes need to be interpreted with caution, this approach allowed us to examine a large, diverse patient population that was admitted to over 300 different institutions in California using ICD-9 coding that has been validated for the identification of sepsis cases.[1,2,13] This is especially relevant, given that our study shows that the likelihood of having a DNR is associated not only with patient-level characteristics, but also with hospital and healthcare system-related factors.

Although there is a paucity of information on the use of DNR orders in sepsis, our findings are consistent with previous studies that examined the epidemiology of DNR orders in mixed patient populations. Zingmond et al. showed that use of early DNR orders in patients admitted with 40 of the most common medical and surgical diagnosis-related groups (DRGs) was affected by hospital size and geographic location, even after accounting for patient characteristics.[9] Among patient characteristics, previous studies showed that being older, White, and having more medical comorbidities increases the likelihood of having a DNR order across multiple medical conditions.[7–9] Using a nationally representative sample of nearly 14,000 Medicare patients, Wenger and colleagues showed that the frequency and the factors that influence DNR use also varied significantly by medical diagnoses.[8] In that study, the rates of DNR use ranged from 4 % in patients admitted with hip fracture to 21 % in those admitted with a cerebrovascular accident. Our study shows that the prevalence of DNR orders in patients hospitalized with sepsis is among the highest for the medical conditions that have been examined to date. Previous studies have shown that the probability of survival is significantly associated with the likelihood of having a DNR order.[6,8,19] This suggests that the higher prevalence of DNR orders in patients with sepsis may be due to the perception of high mortality, in addition to the patient and institutional-related factors identified in our study.[20]

Our study extends the findings of previous investigations by also examining the use of DNR orders longitudinally over the hospitalization. Our results show that hospital and healthcare system-related factors, age, race / ethnicity and gender are less associated with the likelihood of having a DNR order later in the hospitalization. On the other hand, medical comorbidities have a greater association than within the first 24 h. This suggests that early in the hospital course for sepsis, the use of a DNR order is likely determined by a complex interaction between patient preferences, sociodemographic variables, hospital patterns of practice, and the physician's integrated assessment of medical illness, among other factors. However, as the hospitalization continues, the decision of a DNR order is more heavily influenced by the medical condition of the patient.

There are several limitations to our study. First, the observational nature of our study identifies associations, but cannot establish causality. As an example, our results show that ethnic minorities are less likely to receive a DNR order during a hospitalization for sepsis. These findings are consistent with previous studies that identified differences in the delivery of care between White patients and ethnic minorities.[7,21–24] While our findings may suggest possible disparities in care, our data cannot differentiate between whether a DNR was offered and refused, or never offered at all. Furthermore, we cannot determine whether DNR orders were used appropriately for each admission. Given this, our findings are hypothesis-generating and need to be further examined in studies that include more clinical detail regarding the implementation of DNR orders during hospitalizations for sepsis. Specifically, measurements of patient preferences and information regarding how DNR orders were offered to patients and their caregivers would clarify the significance of the associations that have been identified in our study. Second, administrative data and ICD-9 CM discharge codes are not primarily designed for research purposes and may have biases. In order to minimize this bias, we used a case definition of sepsis that was previously validated in the medical literature. Furthermore, the similarity in the rates of DNR use in patients admitted with a CVA in our study compared to those in previous studies support the validity of our approach. Finally, we excluded all admissions in which there were missing data in order to perform a complete case analysis. As this could introduce bias into the study, we analyzed the hospitalizations that were excluded due to data masking, and found that distribution of baseline characteristics and the influence of patient and hospital-associated factors on the use of early and late DNR orders was similar to that of the overall study population (Supplementary Data Figure 1 and Tables 1–3). These analyses, along with the consistency of our findings with the existing literature where overlap exists, support the interpretation that any biases that resulted were small.

In summary, our study shows that the use of DNR orders during hospitalizations for sepsis is associated with multiple patient, hospital, and healthcare system-related factors in addition to patient preferences. Furthermore, over the course of a hospitalization, the burden of medical illness becomes more influential relative to the other factors. Although the associations in our study need to be further examined and better delineated, our findings highlight the fact that interventions to improve the use of DNR orders during hospitalizations for sepsis need to reflect its multidimensional and dynamic influences.

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Dr. Chang: contributed to acquiring, analyzing, and interpreting the data and drafted the submitted article.
Dr. Brass: contributed to analyzing and interpreting the data; reviewed and revised the article critically for important intellectual content.
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