Use of Do-Not-Resuscitate Orders for Critically Ill Patients with ESKD

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ABSTRACT

Background Despite having high comorbidity rates and shortened life expectancy, patients with ESKD may harbor unrealistically optimistic expectations about their prognoses. Whether this affects resuscitation orders is unknown.

Methods To determine whether do-not-resuscitate (DNR) orders differ among patients with ESKD compared with other critically ill patients, including those with diseases of other major organs, we investigated DNR orders on admission to intensive care units (ICUs) among 106,873 patients in the United States.

Results Major organ disease uniformly associated with increased risk of hospital mortality, particularly for cirrhosis (adjusted odds ratio [aOR], 2.67; 95% confidence interval [95% CI], 2.30 to 3.08), and ESKD (aOR, 1.47; 95% CI, 1.31 to 1.65). Compared with critically ill patients without major organ disease, patients with stroke, cancer, heart failure, dementia, chronic obstructive pulmonary disease, and cirrhosis were statistically more likely to have a DNR order on ICU admission; those with ESKD were not. Findings were similar when comparing patients with a single organ disease with those without organ disease. The disconnect between prognosis and DNR use was most notable among Black patients, for whom ESKD (compared with no major organ disease) was associated with a 62% (aOR, 1.62; 95% CI, 1.27 to 2.04) higher odds of hospital mortality, but no appreciable difference in DNR utilization (aOR, 1.06; 95% CI, 0.66 to 1.62).

Conclusions Unlike patients with diseases of other major organs, critically ill patients with ESKD were not more likely to have a DNR order than patients without ESKD. Whether this reflects a greater lack of advance care planning in the nephrology community, as well as a missed opportunity to minimize potentially needless patient suffering, requires further study.

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As modern medicine has extended life expectancy, advance care planning has become an increasingly important cornerstone of medical therapy, maximizing patient autonomy, prioritizing patient centered goals of care, and protecting against overutilization of aggressive measures at the end of life.[1–3] It is particularly important for those with significant comorbidities and shortened life expectancy,

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where the balance between the benefits and risks of intensive medical therapy shifts toward more conservative care.[4,5]

Preference regarding cardiopulmonary resuscitation (CPR) is one of the cardinal decisions addressed by advance care planning, weighing the risks of life-saving measures with the potential for meaningful benefit. For those patients deemed unlikely to benefit from such intense intervention, the use of a do-not-resuscitate (DNR) order may limit overmedicalization,[6] particularly among the elderly and those with major organ disease.[7–9]

Although the modernization of dialysis continues to improve outcomes in ESKD, overall survival remains relatively poor, with an average 5-year mortality of approximately 60%. Nonetheless, patients with ESKD, particularly those who are older with multimorbidity, often paradoxically continue to choose maximal intensity of care even into the last stages of life.[10–12] Whether this contrast between ongoing aggressive care in the face of poor prognosis extends into the most critical moments of disease, namely in the intensive care unit (ICU), remains uncertain. Although greater utilization of the DNR order at ICU admission might be expected in patients at greatest risk for hospital mortality, including those with diseases of major organs, studies have not examined CPR orders in critically ill patients with ESKD, and how they might compare with patients with other diseases.

Accordingly, we examined whether CPR orders on admission to the ICU differ between patients with and without ESKD, and how that compares to those with stroke, cancer, heart failure, dementia, chronic obstructive pulmonary disease (COPD), and cirrhosis. Additionally, we examined whether patients with ESKD admitted with an order for full resuscitation were more likely to have a de-escalation of care to DNR than patients without ESKD.

Significance Statement

Despite having high rates of comorbid illnesses and significantly shortened life expectancy, patients with ESKD may be unrealistically optimistic about their own prognoses. In their study of do-not-resuscitate (DNR) orders upon admission to intensive care in a large sample of critically ill patients from hospitals across the United States, the authors observed more frequent DNR orders among patients with diseases of other major organs compared with patients without major organ disease. However, despite overall higher rates of comorbidity and hospital mortality in patients with ESKD, they found no such difference in the use of DNR orders between patients with and without ESKD. The lower use of DNR orders in this highly comorbid group might reflect a missed opportunity to avoid overmedicalization and unnecessary patient suffering at the end of life.

METHODS

Data Source

Phillips Healthcare, a major vendor of ICU equipment and services, provides a telehealth ICU platform to over 300 hospitals across the United States. Data from participating hospitals is anonymously curated in the electronic Intensive Care Unit Research Institute Database (eICU-RI), a collaborative partnership between Philips Healthcare and the Laboratory of Computational Physiology at Massachusetts Institute of Technology.[13,14] It contains high-resolution patient data, including demographics, vital signs, laboratory tests, illness severity scores, fluid intake and outputs, and diagnostic coding from patients admitted between 2003 and 2016. Participating hospitals trained clinicians to use the Philips Healthcare platform, using primary data entry and drop-down boxes to adjudicate patient information and diagnoses, with direct synchronization with laboratory and clinical data. We used the publicly accessible version of the eICU-RI, which contains data from 131,495 unique first critical illness hospitalizations during 2014 and 2015. We excluded hospital and ICU transfers, leaving 106,873 initial ICU stays for primary analysis.

Primary and Secondary Outcomes

Designation of CPR orders are required order upon ICU admission. We categorized the following orders as DNR: DNR (83%), do not intubate (7%), no CPR (5%), comfort measures only (1%), and other resuscitation order limitations (4%). Secondarily, for those admitted with an order for full resuscitation, we examined those with de-escalation to a DNR order.

Variables

Basic demographics included age, sex, and race/ethnicity. Race/ethnicity was self-reported as White, Black, Hispanic, Asian, Native American, or other/unknown. Admission diagnoses were adjudicated by trained clinicians within the first 24 hours of ICU admission as part of the Acute Physiology and Chronic Health Evaluation IV scoring system, and were categorized into the following categories: acute coronary syndrome, ARF, asthma or COPD, coronary artery bypass grafting, cardiac arrest, chest pain unknown, congestive heart failure (CHF), other cardiovascular disease, coma, stroke, diabetic ketoacidosis, gastrointestinal bleed, gastrointestinal blockage, neurologic disease, overdose, pneumonia, respiratory disease, sepsis, trauma, valve disease, and other. The Charlson comorbidity index classification of comorbid disease was used to identify patients with a history of stroke (with hemiplegia), cancer (leukemia, lymphoma, or solid tumor within 5 years of diagnosis), CHF, dementia, COPD, or cirrhosis.[15] Patients with ESKD were identified through a history of hemodialysis or peritoneal dialysis used as part of the Acute Physiology and Chronic Health Evaluation IV coding score.

Statistical Analyses

Baseline characteristics were presented as percentages for categorical variables and mean and SD for continuous variables according to major organ disease. We used logistic regression to describe the adjusted associations between ESKD and hospital mortality, and ESKD and DNR order utilization on ICU admission, including all variables above and separate indicator variables for each organ disease. Secondarily, because of significant overlap of disease among patients, we created indicator

Table 1. Baseline characteristics according to ESKD status

Baseline characteristics of critically ill patients according to diseases of major organs								
Characteristic	No Major Organ Disease	Stroke	Cancer	CHF	Dementia	COPD	Cirrhosis	ESKD
N[a]	64,093	8099	14,222	13,498	3338	13,935	1517	3022
Age, yr	58.3 (18.5)	70.7 (13.4)	69.7 (13.3)	71.4 (13.7)	81.4 (9.1)	68.9 (11.9)	59.0 (13.2)	62.7 (14.6)
Sex, male	55.5	52.3	53.0	53.1	44.3	51.3	62.3	56.3
Race/ethnicity								
White	76.3	73.6	83.4	77.3	76.7	84.9	75.8	53.2
Black	10.6	15.1	7.8	13.4	10.7	8.3	7.5	27.8
Hispanic	3.9	3.5	2.9	3.3	6.0	2.3	6.1	6.2
Asian	1.8	2.0	1.5	1.2	1.6	0.7	1.7	2.5
Other/unknown	7.4	5.8	4.4	4.8	5.0	3.8	8.9	10.3
Comorbidities								
Stroke	—	—	8.1	12.5	21.6	10.8	5.3	13.3
Cancer	—	14.3	—	13.6	14.2	17.8	12.7	9.7
CHF	—	20.9	12.9	—	21.0	28.2	12.2	30.6
Dementia	—	8.9	3.4	5.2	—	4.1	1.5	2.6
COPD	—	18.5	17.4	29.1	17.2	—	11.3	2.2
Cirrhosis	—	1.0	1.4	1.4	0.7	1.2	—	14.6
ESKD	—	4.5	2.1	6.9	2.4	3.2	4.4	—
Admission diagnosis								
Acute coronary syndrome	8.3	4.5	4.0	4.5	3.0	4.4	0.7	3.6
Coronary artery bypass grafting	4.9	2.9	2.6	3.7	0.5	2.5	0.6	2.6
Cardiac arrest	5.9	5.7	6.1	8.5	6.3	6.6	2.2	8.9
Stroke	8.1	16.1	5.4	4.9	8.9	4.1	2.5	7.2
CHF	1.5	4.7	2.9	15.0	4.0	5.9	2.2	8.6
Gastrointestinal bleed	4.7	5.5	6.4	5.1	5.4	4.8	31.2	6.5
Pneumonia	1.9	3.5	3.2	4.0	6.0	6.5	1.3	2.7
Sepsis	9.0	15.5	16.9	15.6	27.5	18.3	17.3	17.3
Other	55.7	41.6	52.5	38.7	38.4	46.9	42.0	42.6
Mechanical ventilation first day, yr	23.5	23.3	21.3	24.3	19.7	27.3	25.1	22.3
Admission creatinine, mg/dl	1.3 (1.5)	1.7 (1.8)	1.5 (1.5)	2.0 (2.0)	1.7 (1.5)	1.5 (1.5)	1.8 (1.6)	6.9 (3.9)
Charlson comorbidity score	2.1 (1.7)	6.7 (2.3)	6.7 (2.9)	6.1 (2.5)	6.7 (2.2)	5.5 (2.5)	6.7 (2.6)	5.9 (2.4)
APACHE severity illness score	49.9 (25.0)	59.3 (24.6)	59.1 (24.5)	61.7 (24.0)	69.2 (23.7)	58.9 (24.6)	77.6 (29.4)	66.8 (25.6)

Means (SD) for continuous variables and column percentages for categorical variables provided. APACHE, Acute Physiology and Chronic Health Evaluation scoring system.

[a]Although the column for patients without major organ disease represents unique patients, there is significant patient overlap of disease categories. Total cohort size 106,873; 30,630 had only one diseased major organ and 12,150 had more than one diseased major organ.

variables for patients who had only one of the seven major organ diseases, as well as patients with any combination or organ diseases, and examined how their rates and risk of mortality and DNR utilization compared with patients without any major organ disease.

Additionally, among those patients admitted with an order for full resuscitation, we used Cox proportional hazards model to estimate hazard ratios and 95% confidence intervals (95% CIs) for risk of code de-escalation. Time to event was defined as time from admission to either code status change or ICU discharge, censoring deaths or discharges without a code status change.

To examine for selection bias, whereby patients with full-code ESKD might be admitted into the ICU specifically to undergo urgent dialysis, we examined whether CPR orders were related to time from admission to dialysis start among patients on hemodialysis who were dialyzed in the ICU. We also describe whether CPR orders and hospital mortality differed according to dialysis modality (peritoneal versus hemodialysis).

RESULTS

Baseline Characteristics

Patients with ESKD accounted for 3% (n=3022) of critically ill admissions, and tended to be minority with a history of CHF, as well as to have more frequent admissions for cardiac arrest, than patients without ESKD (Table 1). Approximately 8% (n=256) of patients with ESKD were on peritoneal dialysis.

Major Organ Disease and Mortality

Although any disease of a major organ was associated with increased hospital mortality as compared with those without disease, those with cirrhosis and ESKD had the highest rates

Table 2. Rates and unadjusted and adjusted odds of hospital mortality and of a DNR order on admission to the ICU per major organ disease, compared with patients with no organ disease

Characteristic	No Major Organ Disease	Stroke	Cancer	CHF	Dementia	COPD	Cirrhosis	ESKD
N	64,093	8099	14,222	13,498	3338	13,935	1517	3022
Hospital mortality								
n (%)	3929 (6.1)	861 (10.6)	1649 (11.6)	1592 (11.8)	487 (14.6)	1,558 (11.1)	250 (16.4)	394 (13.0)
Unadjusted	Reference	1.23 1.15 to 1.33	1.58 1.49 to 1.67	1.46 1.37 to 1.54	1.87 1.69 to 2.06	1.35 1.28 to 1.44	2.33 2.02 to 2.67	1.60 (1.43 to 1.78)
Adjusted	Reference	1.05 0.97 to 1.14	1.35 1.27 to 1.43	1.16 1.09 to 1.23	1.11 1.01 to 1.23	1.18 1.11 to 1.26	2.67 2.30 to 3.08	1.47 1.31 to 1.65
DNR order on admission to the ICU								
n (%)	1957 (3.1)	815 (10.1)	1202 (8.5)	1365 (10.1)	827 (24.8)	1205 (8.7)	77 (5.1)	166 (5.5)
Unadjusted	Reference	1.64 1.51 to 1.79	1.76 1.65 to 1.89	1.96 1.83 to 2.09	5.85 5.36 to 6.37	1.51 1.40 to 1.61	1.03 0.81 to 1.30	0.89 0.76 to 1.05
Adjusted	Reference	1.32 1.21 to 1.43	1.29 1.21 to 1.39	1.29 1.20 to 1.38	2.19 2.00 to 2.40	1.19 1.10 to 1.28	1.38 1.07 to 1.75	1.16 0.98 to 1.37

Data are displayed as odds ratio with 95% CI. Adjusted for age, sex, race/ethnicity, admission diagnosis, and the other major organ diseases. Reference category is critically ill patients without organ disease.

and adjusted risk (Table 2). Among patients with a single organ failure documented, those with cirrhosis and ESKD similarly had the highest risk (Table 3).

Major Organ Disease and DNR Utilization

The highest rates of DNR utilization were observed among patients with dementia. Diseases of other major organs were similarly more likely to have a DNR order, except for ESKD, where no significant association was observed (adjusted odds ratio, 1.16; 95% CI, 0.98 to 1.37) compared with those without major organ disease (Table 2). Among patients with single organ failure, all diseases except for ESKD were associated with higher DNR utilization, whereas patients with ESKD actually used a DNR order less frequently than critically ill patients without any major organ disease (2.8% versus 3.1%, respectively) (Table 3).

Effect of Race on the Association between ESKD and DNR Utilization

Black patients had the lowest rates of DNR order utilization among racial and ethnic groupings (Figure 1). The discrepancy between higher hospital mortality yet lower DNR utilization observed among patients with ESKD was most apparent among Black patients, although not statistically different (multiplicative interaction term between Black race and ESKD P values both >0.05 for mortality and DNR utilization) (Table 4). Among other racial/ethnic groupings, patients with ESKD had 46% (95% CI, 1.28 to 11.69) higher odds of hospital mortality and 22% (95% CI, 1.00 to 1.46) higher odds of DNR utilization than patients without major organ diseases. In contrast, among Black patients, ESKD conferred no appreciable difference in DNR utilization (odds ratio, 1.06; 95% CI, 0.66 to 1.62) despite 62% (95% CI, 1.27 to 2.04) higher odds of hospital mortality.

De-escalation of Code Status

Among 101,163 patients with a full resuscitation order on admission, 8% (n=8519) had a change to DNR during hospitalization. This occurred more frequently among patients with ESKD than those without ESKD (12.0% [n=342] versus 8% [n=8177]). The average time to code status change was 42.3 ($\pm$51.1) hours. In adjusted analysis, patients with ESKD were 43% (hazard ratio, 1.43, 95% CI, 1.20 to 1.49) more likely to de-escalate from full resuscitation to DNR than patients without ESKD, similarly to other diseases of major organs.

Sensitivity Analyses

Among 1687 patients on hemodialysis who underwent dialysis in the ICU, time from ICU admission to dialysis treatment initiation did not differ between those with an admission order for full resuscitation versus DNR (9.9$\pm$26.9 versus 10.3$\pm$22.6 hours; P=0.89). Neither DNR utilization (95.3% versus 94.4%) nor hospital mortality (13.0% versus 13.1%) differed between patients undergoing peritoneal and hemodialysis, respectively.

Table 3. Rates and unadjusted and adjusted odds of hospital mortality and of a DNR order on admission to the ICU in patients with single or multiple organ diseases, compared with those with no organ disease

Characteristic	No Major Organ Disease	Stroke only	Cancer only	CHF only	Dementia only	COPD only	Cirrhosis only	ESKD only	More Than One Organ Disease
N	64,093	4074	9294	6442	1529	6863	983	1445	12,150
Hospital mortality									
n (%)	3929 (6.1)	340 (8.3)	970 (10.4)	641 (10.0)	200 (13.1)	643 (9.4)	149 (15.1)	162 (11.2)	1640 (13.5)
Unadjusted	Reference	1.40 1.24 to 1.56	1.78 1.65 to 1.92	1.69 1.55 to 1.85	2.32 2.00 to 2.71	1.58 1.45 to 1.72	2.75 2.29 to 3.27	1.93 1.63 to 2.27	2.39 2.29 to 3.26
Adjusted	Reference	1.03 0.91 to 1.16	1.45 1.33 to 1.56	1.20 1.09 to 1.31	1.17 0.99 to 1.36	1.24 1.13 to 1.36	2.98 2.47 to 3.59	1.60 1.33 to 1.89	1.58 1.47 to 1.68
DNR order on admission to the ICU									
n (%)	1957 (3.1)	304 (7.5)	614 (6.6)	511 (7.9)	353 (23.1)	421 (6.1)	32 (3.3)	41 (2.8)	1477 (12.2)
Unadjusted	Reference	2.50 2.26 to 2.90	2.24 2.04 to 2.46	2.73 2.47 to 3.02	9.53 8.38 to 10.8	2.07 1.86 to 2.31	1.07 0.73 to 1.49	0.92 0.67 to 1.25	4.39 4.09 to 4.71
Adjusted	Reference	1.54 1.34 to 1.76	1.46 1.32 to 1.61	1.44 1.29 to 1.61	2.52 2.20 to 2.89	1.28 1.13 to 1.43	1.41 1.32 to 1.61	1.02 0.73 to 1.39	1.99 1.84 to 2.15

Data are displayed as odds ratio with 95% CI. Adjusted for age, sex, race/ethnicity, admission diagnosis, and the other major organ diseases. Reference category is critically ill patients without organ disease.

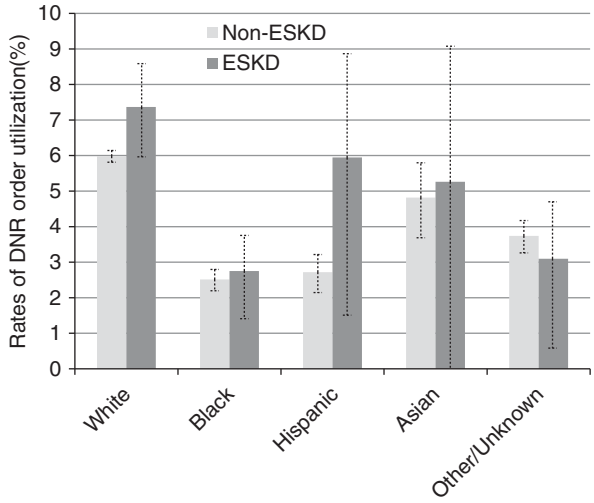

Figure 1. Lower rates of DNR utilization among Blacks with ESKD. *P* values for differences between non-ESKD and ESKD DNR order utilization per ethnic group were as follows: White, *P*=0.03; Black, *P*=0.67; Hispanic, *P*=0.01; Asian, *P*=0.86; and other/unknown, *P*=0.54.

DISCUSSION

Despite high rates of comorbidity and in-hospital mortality, patients with ESKD were not significantly more likely to utilize a DNR order on admission to the ICU than patients without major organ disease. This contrasts with the significantly higher utilization of DNR orders among patients with stroke, cancer, CHF, dementia, COPD, and cirrhosis. Simultaneously, patients with ESKD were more likely to have a subsequent de-escalation of care and die during the critical illness hospitalization than patients without major organ disease.

Although not statistically significant, the contrast between poor hospital prognosis yet low DNR utilization among patients with ESKD was most notable among Black patients, for whom those with ESKD had a 62% higher odds of hospital death but no difference in DNR utilization than patients without major organ disease. This compared with a 46% and 22% higher risk of death and DNR utilization, respectively, among other race/ethnicities. Although lower DNR utilization might reflect less advance care planning among Black patients,[16–20] including those with kidney disease,[21,22] we have also recently used the same Philips Healthcare data set to demonstrate racial disparities in critical care access.[23] Accordingly, the effect of prehospital practices, such as primary care[24,25] and health literacy,[26] versus the effect of within hospital practices, such as the counseling of admitting physicians, on resuscitation orders is uncertain. Regardless of the mechanisms, Black patients may be at particular risk for overmedicalization.

The higher rate of comorbidity and risk of hospital mortality among patients with ESKD underscores the vulnerability of this population, who accordingly might derive particular benefit from advance care planning. Yet despite palliative

Table 4. Adjusted odds of hospital mortality and of a DNR order on admission to the ICU per major organ disease, compared with patients with no organ disease, among Black patients and other races/ethnicities

Characteristic		No Major Organ Disease	Stroke	Cancer	CHF	Dementia	COPD	Cirrhosis	ESKD
Black	Mortality	Reference	0.91 (0.72 to 1.12)	1.61 (1.31 to 1.98)	1.05 (0.86 to 1.26)	1.01 (0.72 to 1.39)	1.07 (0.85 to 1.33)	1.70 (0.86 to 3.09)	1.62 (1.27 to 2.04)
	DNR	Reference	1.21 (0.89 to 1.65)	1.60 (1.16 to 2.18)	1.55 (1.15 to 2.06)	2.31 (1.62 to 3.27)	1.28 (0.91 to 1.76)	1.51 (0.44 to 3.85)	1.06 (0.65 to 1.62)
Other race/ ethnicities	Mortality	Reference	1.07 (0.98 to 1.16)	1.33 (1.25 to 1.41)	1.16 (1.09 to 1.25)	1.13 (1.01 to 1.27)	1.19 (1.11 to 1.27)	2.76 (2.36 to 3.21)	1.46 (1.28 to 1.69)
	DNR	Reference	1.32 (1.21 to 1.45)	1.27 (1.18 to 1.37)	1.29 (1.19 to 1.38)	2.20 (2.00 to 2.42)	1.19 (1.10 to 1.28)	1.40 (1.07 to 1.80)	1.22 (1.00 to 1.47)

Data are displayed as odds ration with 95% CI. Adjusted for age, sex, race/ethnicity, admission diagnosis, and the other major organ diseases. Reference category is critically ill patients without organ disease. Neither mortality or DNR utilization was statistically different among Black patients than other race/ethnicities (multiple *P* value interactions >0.05). Six thousand sixteen (number of patients) with other or unknown racial/ethnic categorization excluded for this analysis.

nephrology championing the need for such discussions,[27–31] barriers still exist. Unrealistic prognostic expectations among patients with ESKD can thwart meaningful conversations about goals of care,[32–34] as does the absence of widespread palliative nephrology training[35,36] and resources.[37] In addition, despite validated prognostication tools,[38] discussions about prognosis, goals of care, and dialysis withdrawal are both challenging and time consuming.[39–41] Furthermore, the industrialization of dialysis, including for-profit dialysis providers, transportation companies, physician reimbursement, and other infrastructure, tends to support ongoing dialysis.

Whether the lower utilization of a DNR order on admission among patients with ESKD, combined with higher rates of subsequent de-escalation to DNR in those admitted with a full resuscitation order, directly contributed to patient suffering through medicalization without a meaningful chance of benefit, cannot be ascertained from our study. However, our findings are in keeping with other studies that suggest the higher treatment intensity continues close to the end of life among patients with ESKD,[42,43] potentially reflecting a missed opportunity to minimize exposure to futile care.

Our analysis has important limitations. We had no information about pre-ICU illness or care. However, potential confounding owing to the absence of premorbid information is not particular to patients with ESKD, and likely would uniformly apply to other diseases, limiting the potential for bias in our analysis. Selection bias, whereby the dialysis procedure itself might influence the decision for ICU admission, could influence our results, although code status was not associated with differences in time to dialysis initiation. In addition, the overall mortality rates among participating ICUs was lower than reported in other ICU settings, reflecting the community nature of many of the participating ICUs. Whether the observed differences in DNR utilization extend to referral centers with higher acuity of illness remains to be explored. Among patients admitted for critical care, patients with ESKD are as likely to have admission orders for full resuscitation as patients without major organ disease, in contrast to the higher DNR utilization observed among patients with a history of stroke, cancer, CHF, dementia, COPD, and cirrhosis. Simultaneously, patients with ESKD are more likely to subsequently de-escalate care and to die within the hospital stay. This contrast between poor prognosis yet low DNR utilization is most notable among Black patients. Whether more comprehensive advance care planning in ESKD might limit medical overutilization and prevent unnecessary suffering requires further study.

DISCLOSURES

All authors have nothing to disclose.

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See related editorial, "Do-Not-Resuscitate Orders among Patients with ESKD Admitted to the Intensive Care Unit: A Bird's Eye View," on pages 2232–2234.