DNR directives are established early in mechanically ventilated intensive care unit patients

[Les directives PDR sont établies tôt chez les patients sous ventilation mécanique à l'unité des soins intensifs]

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Purpose: Setting treatment goals in the intensive care unit (ICU) often involves resuscitation decisions. Our objective was to study the rate of establishing do-not-resuscitate (DNR) directives, determinants, and outcomes of those directives for mechanically ventilated patients.

Methods: In a multicentre observational study, we included consecutive adults with no DNR directives within 24 hr of ICU admission who were mechanically ventilated for at least 48 hr. We identified the rate with which DNR directives were established, and factors associated with these directives.

Results: Among 765 patients, DNR directives were established for 231 (30.2%) patients; 143 (62.1%) of these were established within the first week. Factors independently associated with a DNR directive were: patient age [≥ 75 yr (hazard ratio [HR] 2.3, 95% confidence interval 1.5–3.4], 65 to 74 yr (HR 1.8, 1.2–2.7), 50 to 64 yr (HR 1.4, 1.0–2.2) relative to < 50 yr); medical rather than surgical diagnosis (HR 1.8, 1.3–2.5); multiple organ dysfunction score (HR 1.7 for each five-point increment, 1.4–2.0); physician prediction of ICU survival [< 10% (HR 15.0, 6.7–33.6)], 10 to 40% [(HR 5.0, 2.3–11.2), 41 to 60% (HR 4.0, 1.8–9.0) relative to > 90%]; and physician perception of patient preference to limit life support (no advanced life support [(HR 5.8, 3.6–9.4) or partial advanced life support (HR 3.2, 2.2–4.6) compared to full measures].

Conclusion: One third of mechanically ventilated patients had DNR directives established early during their ICU stay after the first 24 hr of admission. The strongest predictors of DNR directives were physician prediction of low probability of survival, physician perception of patient preference to limit life support, organ dysfunction, medical diagnosis and age.

Objectif : *Le choix des objectifs de traitement à l'unité des soins intensifs (USI) comprend souvent des décisions concernant la réanimation. Notre but était d'étudier le taux d'ordonnance «pas de réanimation» (PDR), les déterminants et les conséquences de ces directives pour les patients ventilés mécaniquement.*

Méthode : *Lors d'une étude par observation multicentrique, nous avons inclus des adultes pour qui la directive PDR avait été émise au cours des 24 premières heures de présence à l'USI et qui étaient sous ventilation mécanique depuis au moins 48 h. Nous avons déterminé le taux de directives PDR établies et les facteurs qui y sont associés.*

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Résultats : *Parmi 765 patients, il y a eu des directives PDR dans 231 (30,2 %) des cas ; 143 (62,1 %) d'entre elles à l'intérieur de la première semaine. Les facteurs indépendamment associés à la directive PDR ont été : l'âge du patient [= 75 ans (risque relatif [RR] de 2,3, intervalle de confiance de 95 % 1,5–3,4], 65 à 74 ans (RR de 1,8, 1,2–2,7), 50 à 64 ans (RR de 1,4, 1,0–2,2) par rapport à < 50 ans) ; le diagnostic médical plutôt que chirurgical (RR de 1,8, 1,3–2,5) ; le score de défaillance multiviscérale (RR de 1,7 pour chaque palier de cinq points, 1,4–2,0) ; la prédiction de survie à l'USI selon le médecin [< 10 % (RR de 15,0, 6,7–33,6)], 10 à 40 % [(RR de 5,0, 2,3–11,2), 41 à 60 % (RR de 4,0, 1,8–9,0) par rapport à > 90 %] ; la perception du médecin de la préférence du patient face aux limites du maintien de la vie (par de maintien poussé [(RR de 5,8, 3,6–9,4) ou maintien poussé partiel (RR de 3,2, 2,2–4,6) comparé aux pleines mesures].*

Conclusion : *Des directives PDR sont établies tôt pendant le séjour à l'USI, 24 h ou plus après l'admission, chez un tiers des patients ventilés mécaniquement. Les prédicteurs les plus puissants de directives PDR sont la prédiction du médecin d'une faible probabilité de survie, la perception du médecin de la préférence du patient face à la limite du maintien de la vie, la dysfonction organique, le diagnostic médical et l'âge.*

SETTING realistic treatment goals in the intensive care unit (ICU) often involves decisions about whether to attempt cardiopulmonary resuscitation (CPR) in the event of a cardiopulmonary arrest. Hospital survival rates of ICU patients who receive CPR range from 0 to 33%.[1–7] Decisions to provide or forgo CPR in the ICU should reflect patients' values and preferences. The influence of physicians' judgements about the utility of CPR on patients' resuscitation preferences remains uncertain, as does the effect of physicians' perceptions of patients' survival and of patients' preferences on decisions to offer CPR.

Before making decisions about CPR and other life-support measures, many patients want to discuss their prognosis with physicians.[8–12] Despite discussions, physicians and patient surrogates are still sometimes unaware of, or are unable to predict, patient preferences regarding CPR.[12–16] Moreover, the concurrence between physician or surrogate judgements and patients' CPR preferences is low.[10,12,14,16] For critically ill patients already receiving life-support who cannot communicate their values and preferences, it is often unclear whether CPR would be congruent with their wishes. In the ICU, decisions about CPR are frequently delayed until late in the course of critical illness[12] and sometimes actually follow rather than precede cardiopulmonary arrest and successful resuscitation.[17]

When critically ill patients elect not to undergo CPR in the event of a cardiopulmonary arrest, their wishes are documented as do-not-resuscitate (DNR) directives. Prospective studies have shown that 9 to 13% of patients had DNR orders written at some point during their ICU stay.[18–20] Also, the frequency of new DNR orders in the ICU appears to have increased over the past decade.[21,22] We previously found that explicit CPR directives were established for only 11% of ICU patients within the first 24 hr of their ICU admission; half of these were directives not to resuscitate.[23] Increased age, illness severity, and inability to participate in decision-making were the strongest predictors of a DNR directive during the first 24 hr of ICU admission.[23] The clinical decisions that lead to establishing DNR directives may change with time during the ICU course. To further understand this process, the objectives of this study were to examine the rate, determinants and outcomes of DNR directives for mechanically ventilated patients after the first 24 hr of their ICU stay.

Methods

Patients and procedures

Among the 3,099 critically ill patients admitted to the 15 ICUs (11 in Canada, two in the US, one in Sweden and one in Australia) between May 1995 and September 1998, of the originally published study,[23] we included consecutive patients in this study if they met the following criteria: age greater than 18 yr, predicted ICU length of stay greater than 72 hr, and mechanical ventilation for at least 48 hr. Patients were excluded if they had a DNR directive established before or within the first 24 hr of ICU admission. If patients had more than one ICU admission, we included only the last. The need for informed consent was waived due to the observational nature of the study. Ethics approval was obtained by all Institutional Ethics Review Boards.

We collected baseline data including patient sex, age, APACHE II score[24] during the first ICU day, and admission diagnosis. Daily, we calculated the multiple organ dysfunction score (MODS),[25,26] and recorded whether life support (mechanical ventilation, inotropes or vasopressors, dialysis) was administered, withheld or withdrawn, the patient's ability to participate in decision-making, and whether a DNR directive was established. In addition, we documented daily the attending physicians' clinical judgements, including their estimate of the patient's prior function, their perception of the patient's preference regarding limitation of life-support, their prediction of the patient's ICU and hospital survival, and their prediction of the

patient's functional and cognitive status one month after hospital discharge. The primary outcome was a DNR directive established during the ICU stay, more than 24 hr after ICU admission. All patients were followed until hospital discharge.

Statistical analysis

We present continuous variables as means and standard deviations (± SD) or medians and interquartile range (IQR) for skewed data. We report rates using proportions and 95% confidence intervals. Using life table analysis, we established the hazard rate for establishing DNR directives. We compared the differences in important patient characteristics and outcomes between patients with and without DNR directives. To further characterize patients for whom DNR directives were established in the ICU, we categorized these patients into those who underwent withdrawal of at least one form of life-support and those who did not.

To determine the factors associated with DNR directives established during the ICU admission, we used a Cox proportional hazards regression analysis for time-dependent outcomes and time-dependent explanatory variables.[27] We identified six baseline factors potentially associated with DNR decisions including patient age (< 50 yr, 50–64 yr, 65–74 yr, ≥ 75 yr), sex, APACHE II score (five unit interval), medical *vs* surgical admitting diagnosis, physician's estimation of patient's prior functional status (poor, moderate, good), and patient's ability to participate in decisions. In addition, daily factors were included in the univariable analysis, excluding values 24 hr before the DNR directive: illness severity factors [MODS (five unit interval), inotropes, hemodialysis], physician's clinical judgements [physician prediction of ICU and hospital survival (< 10, 10–40%, 41–60%, > 60%)], physician prediction of patient's future functional status and future cognitive function one month after hospital discharge (don't believe patient will leave hospital, severely limited, somewhat limited, totally independent), physician perception of patient preference to limit lifesupport (no advanced life-support, partial advanced life-support, full advanced life-support), and centre. We tested for all pairwise interactions among the daily factors in the multivariable model and their interactions with time, and tested the proportional hazards assumption of all variables using the time-dependent covariate function.[27]

All factors in the univariable analysis associated with DNR directives with a P value < 0.1 were entered into the full multivariable model. We then used a forward stepwise likelihood ratio method for the final multivariable analysis. We ordered the variables to include patient factors, centre, and then physician clinical judgements. Variables were retained in the final model if $P < 0.01$. These analyses were performed using SPSS 11.0™ (Chicago, IL, USA).

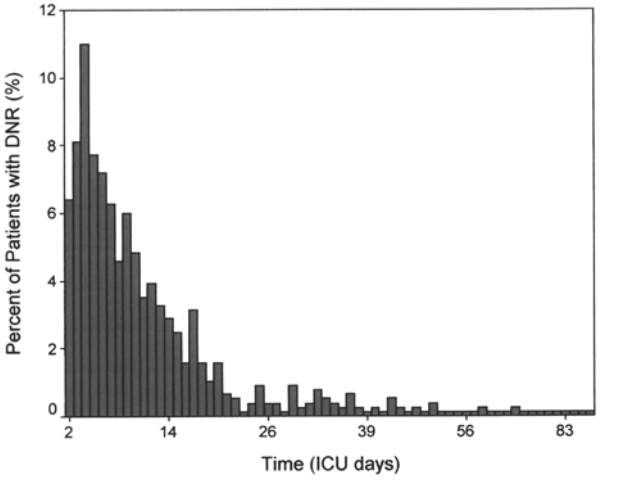

FIGURE We present the day in the ICU on which new DNR directives were established for 231 of the total of 765 mechanically ventilated patients. The peak rate of establishing DNR directives was on day four of the ICU stay. DNR = do-not-resuscitate; ICU = intensive care unit.

Results

Of 3,099 patients included in the original cohort,[23] 851 were predicted to have an ICU stay of > 72 hr and were mechanically ventilated for > 48 hr. Of these 851 patients, 86 were excluded as they had an explicit CPR directive established either before or during the first 24 hr of ICU admission. Thus, we included 765 patients in this study with a mean age of 60.0 (± 17.7) yr, and a mean APACHE II score of 21.2 (± 8.5). Other baseline characteristics are presented in Table I.

A DNR directive was established for 231 (30.2%) of the 765 patients after the first 24 hr of their ICU stay. Of these 231 directives, 118 (51.2%) were established by day eight (IQR 4–14), and 143 (62.1%) were established by day ten (Figure). The hazard rate for the establishment of a DNR directive in the ICU was constant over the first 40 days of ICU admission and decreased gradually after day 50. Of 231 patients with a DNR directive, the decision-making ability of the patient the day prior to the DNR order was recorded for 205 patients; of these 205 patients, 185 (90.2%) were judged to be unable to participate in decision-making.

TABLE I Baseline characteristics and outcomes

Characteristic or outcome	*Value (n = 765)*
Age (mean ± SD)	60.0 ± 17.7
Female (*n*, %)	324 (42.4)
Admission APACHE II score (mean ± SD)	21.2 ± 8.5
Medical admission (*n*, %)	542 (70.8)
Surgical admission (*n*, %)	223 (29.2)
- Elective surgery	163 (73.1)
- Emergency surgery	60 (26.9)
Admitting diagnosis by category (n, %)	
- Cardiac-medical	83 (10.8)
- Cardiac-surgical	52 (6.8)
- Pulmonary-medical	201 (26.3)
- Pulmonary-surgical	23 (3.0)
- Gastrointestinal-medical	55 (7.2)
- Gastrointestinal-surgical	68 (8.9)
- CNS-medical	75 (9.8)
- CNS-surgical	23 (3.0)
- Sepsis	55 (7.2)
- Trauma	43 (5.6)
Metabolic and miscellaneous	87 (11.4)
DNR orders established during ICU stay (*n*, %)	231 (30.2)
ICU LOS (median, IQR)	9 (5, 16)
ICU mortality (*n*, %)	248 (32.4)
- Died on mechanical ventilation (*n*, %)	138 (55.6)
- Withdrawal of mechanical ventilation (*n*, %)	110 (44.4)
Hospital length of stay (median, IQR)	17 (9, 38)
Hospital mortality (*n*, %) (includes ICU mortality)	294 (38.4)

In this table we present patient baseline characteristics and outcomes in this cohort of 765 patients mechanically ventilated for at least 48 hr and no DNR order established by 24 hr of ICU admission. Hospital mortality includes patients who died in the ICU. SD = standard deviation; APACHE II score = acute physiologic and chronic health evaluation II score; CNS = central nervous system; DNR = do-not-resuscitate; ICU = intensive care unit; LOS = length of stay; IQR = interquartile range.

Mechanically ventilated patients who had DNR directives established after 24 hr of intensive care were significantly older and had a higher severity of illness score on admission to the ICU than those who never had a DNR directive established. They were more likely to undergo withdrawal of mechanical ventilation (99/231 *vs* 26/534, $P < 0.001$) or inotropes (75/231 *vs* 25/534, $P < 0.001$). In addition, patients with DNR directives were more likely to die in the ICU (170/231 *vs* 78/534, $P < 0.001$) or elsewhere in the hospital (21/231 *vs* 25/534, $P < 0.001$), and thus have a shorter hospital length of stay (Table II). Patients with new DNR directives established and at least one form of life-support withdrawn (compared to DNR patients without any withdrawal of life-support), were less likely to be weaned successfully from mechanical ventilation, and had higher ICU and hospital mortality. For DNR patients who ultimately had life-support withdrawn, more than half had one modality withdrawn; mechanical ventilation was the modality most commonly withdrawn (Table II).

In Table A (available as Additional Material at www.cja-jca.org) we present the univariable analysis, and factors derived from the full multivariable analysis associated with a DNR directive established over the ICU stay. All factors met the assumptions of proportional hazards. We did not find any interactions with time, or any differences among centres. We found that five factors were independently associated with establishing a DNR directive in the ICU: patient age [hazard ratio (HR) for ≥ 75 yr 2.3 (95% CI 1.5–3.4), HR for 65 to 74 yr 1.8 (1.2–2.7)], HR for 50–64 yr 1.4 (1.0–2.2) relative to < 50 yr), medical rather than surgical diagnosis (HR 1.8, 1.3–2.5), MODS (HR 1.7 (1.4–2.0) for each five unit increase), physician prediction of ICU survival (predicted probability < 10% HR 15.0 (6.7–33.6); 10 to 40% HR 5.0 (2.3–11.2), 41 to 60% HR 4.0 (1.8–9.0), 61 to 90% HR 1.7 (0.7–4.0) relative to predicted probability of ICU survival > 90%), and physician perception that the patient preferred to limit life-support (no advanced life-support HR 5.8 (3.6–9.4), or partial advanced life-support HR 3.2 (2.2–4.6) compared to full life-support measures).

Discussion

In this multicentre study of mechanically ventilated patients with no DNR directive within 24 hr of admission to ICU, we found that a DNR directive was established for 30% of patients. Approximately 50% of the DNR directives were established in the first week of the ICU stay. In our study, DNR directives were established earlier than in studies from the 1990's, in which they were often documented late in the course of critical illness, just before withholding or withdrawal of lifesupport measures,[12,19,28] or just after a cardiopulmonary arrest.[17] Our results are similar to a recent large European study in which limitation of life sustaining therapy occurred a median of three days after ICU admission.[29] The current trend towards earlier decisions about CPR compared to the past may represent temporal changes in ICU practice, particularly regarding end-of-life care.

We found that the factor most strongly associated with the decision to establish a DNR directive was the physician's prediction of patients' survival. It is surprising that it was not only physician predictions of high likelihood of death that was associated with DNR directives, but also moderate likelihood of death.

TABLE II Patient outcomes for patients with and without a do-not-resuscitate order

Variable	*No DNR during ICU (n = 534)*	*DNR during the ICU stay (n = 231)*		*P value for difference between no DNR and DNR group*
		Withdrawal of at least one form of life-support (n = 134)	*No Withdrawal of life-support (n = 97)*	
Age [mean (SD), yr]	58.2 ± 18.2	64.2 ± 15.1	63.8 ± 6.6	< 0.001
Female [*n* (%)]	213 (39.9)	64 (47.8)	46 (47.4)	0.022
APACHE II score [mean (SD)]	19.9 ± 8.5	25.6 ± 8.1	22.7 ± 7.3	< 0.001
Use of inotropes/vasopressors [*n* (%)]	257 (48.1)	104 (77.6)	64 (66.0)	< 0.001
Use of dialysis [*n* (%)]	38 (7.1)	21 (15.7)	2 (2.1)	0.24
Withdrawal of life-support	N/A			
- Withdrawal of inotropes or vasopressors [*n* (%)]	25 (4.7)	75 (56.0)		< 0.001
- Withdrawal of dialysis [*n* (%)]	0 (0.0)	10 (7.5)		< 0.001
- Withdrawal of mechanical ventilation [*n* (%)]	26 (4.9)	99 (73.9)		< 0.001
Withdrawal of no forms of life-support [*n* (%)]	432 (80.9)	N/A	97 (100)	< 0.001
Withdrawal of one form of life-support [*n* (%)]	2 (0.4)	73 (54.5)	N/A	< 0.001
Withdrawal of two forms of life-support [*n* (%)]	4 (2.6)	43 (32.1)	N/A	< 0.001
Withdrawal of three forms of life-support [*n* (%)]	24 (4.5)	9 (6.7)	N/A	< 0.001
Weaned successfully from mechanical ventilator [*n* (%)]	459 (86.0)	2 (1.5)	50 (51.5)	< 0.001
Died on mechanical ventilator [*n* (%)]	49 (9.2)	33 (24.6)	47 (48.5)	< 0.001
ICU length of stay [median (IQR)]	9 (5, 15)	8 (4, 13)	11 (6, 21)	0.98
Hospital length of stay [median (IQR)]	21 (11, 44)	8 (5, 14)	19 (8, 8, 30)	< 0.001
ICU mortality [*n* (%)]	78 (14.6)	118 (88.1)	52 (53.6)	< 0.001
Hospital mortality [*n* (%)] for patients discharged from ICU	25 (4.7)	10 (7.5)	11 (11.3)	< 0.001
Hospital mortality [*n* (%)] including ICU mortality	103 (19.3)	128 (95.5)	63 (64.9)	< 0.001

In this table we present patient outcomes comparing patients with new DNR orders and no DNR orders established in the ICU, after the first 24 hr. Weaned from mechanical ventilator refers to patients successfully extubated. Withdrawal of mechanical ventilator refers to discontinuation of mechanical ventilation regardless of patient's ability to breathe spontaneously. SD = standard deviation; APACHE II score = acute physiologic and chronic health evaluation II score; DNR = do not resuscitate; ICU = intensive care unit; N/A = not applicable.

While the odds of a DNR decision increased fifteenfold when clinicians predicted ICU survival of < 10% (compared to probability of surviving of > 90%), the odds increased fivefold with predictions of between 10 and 40% probability of ICU survival, fourfold with 41 to 60% probability of ICU survival, and almost twofold with 61 to 90% probability of ICU survival (Table A, available as Additional Material at www.cja-jca.org). We hypothesize that regardless of the patient's probability of surviving critical illness, if and when physicians believe that CPR is unlikely to be successful in the event of a cardiopulmonary arrest during the ICU course, they may convey their beliefs to families in a manner that significantly influences the DNR decision. Thus, over the course of the ICU admission, a model of shared decision-making may evolve between physicians and surrogate decision-makers such that a DNR directive is ultimately established.

The association of DNR directives with age is another important finding of this study. This relationship was not restricted to the elderly, but was also true of patients over 50 yr of age. We previously found that age was strongly associated with DNR decisions made within 24 hr of ICU admission.[23] In contrast, in the previous study we did not find that age was an independent determinant of the decision to withdraw mechanical ventilation.[30] These findings suggest differences in the process of decision-making between DNR directives and life-support withdrawal, in that age appears to influence resuscitation plans in the

event of a cardiopulmonary arrest, but is much less likely to influence the more complex decisions to withdraw life-support.

We previously found that severe premorbid functional impairment was associated with DNR directives established during the first 24 hr of ICU admission.[31] However, in the current study, we found no independent association between prior functional status and DNR directives. An inconsistent relationship between functional status and resuscitation decisions has been identified in other studies, some of which have found an association,[13] while others have not.[32] One potential explanation for the discrepancy between the determinants of initial and subsequent resuscitation decisions in the ICU is that prior functional status may influence initial plans to limit resuscitation in the event of cardiopulmonary arrest. However, as the course of critical illness evolves and the ICU team becomes familiar with the patient, resuscitation decisions in the event of a cardiopulmonary arrest, and subsequent withdrawal of life-support are influenced more strongly by perceptions of patient preferences, and physician predictions about survival and future cognitive function.[30]

There are other important differences and similarities between the determinants of DNR directives established within the first 24 hr of ICU admission[23] compared with those following 24 hr of ICU admission, as we have found in this study. Similar to the first 24 hr of ICU admission,[23] we also found that medical (compared to surgical) diagnosis was an important determinant of a DNR directive. However, unlike the first 24 hr of ICU admission, patients' inability to participate in resuscitation discussions was not found to be a significant predictor of DNR directives following 24 hr of ICU admission. We did not test whether the presence of a legal power of attorney, or the day and time of ICU admission were predictors of DNR directives following 24 hr of ICU admission.

Our results build on the findings of the original SUPPORT study of 6,802 seriously ill hospitalized patients.[12] Multivariable regression analysis of that cohort[13] found that older age, patient self-reported prior functional impairment and prior quality of life, the probability of survival for two months based on the SUPPORT prognostic model, and the patients' stated preference for CPR were associated with early DNR decisions. In two prospective multicentre ICU studies performed more than a decade ago in the United States, severity of illness based on the APACHE II system was the factor most strongly associated with DNR decisions during the ICU admission; older age and prior poor functional status were also associated.[18,33] Therefore, although clinical practice and societal values may change over time, our study affirmed earlier findings that age and illness severity, as measured by organ dysfunction, remain important determinants of DNR directives established after ICU admission.

While our prior study of the likelihood of establishing DNR decisions during the first 24 hr of ICU admission found systematic differences between centres,[23] we found no significant between-centre differences in this study. These results also contrast with a recent large, multicentre, prospective observational, European study (ETHICUS; 29) in which regional religious and cultural differences were explored more fully, and proved to be important determinants of decisions regarding limitations of life-sustaining therapies. We did not assess the influence of cultural or religious diversity on DNR directives in our study. Whether the findings of the ETHICUS study[29] are generalizable to North America is a worthy consideration for future research.

Strengths of this study include a focus exclusively on a cohort of heterogeneous mechanically ventilated ICU patients. A prospective multicentre design, enrollment of 765 patients in 15 centres, comprehensive data collection, and complete follow-up increase the precision of our findings. We used a Cox proportional hazards regression analysis to examine the baseline and time dependent factors most strongly associated with DNR directives, and we described the life-support withdrawal and outcomes of these patients.

This study has several limitations. We did not include patient comorbid illness as a potential predictor of DNR directives. In addition, we did not use a validated instrument to record physicians' perceptions of patients' prior functional status or physicians' predictions of patients' future survival. We did not validate physician predictions of future functional status with an assessment of patients' actual functional status following ICU discharge. The generalizability of these results is strongest for patients treated in similar university-affiliated centres.

In summary, we found that many DNR directives for mechanically ventilated patients occur within the first week of an ICU admission, suggesting a pattern of documenting important end-of-life treatment preferences earlier in the course of critical illness than previously reported. Among patients with DNR orders during their ICU stay who do not undergo withdrawal of life-support, as part of a terminal weaning plan, one third survive their hospitalization, underscoring how factors other than the probability of survival determine these decisions. We showed that the independent factors associated with DNR decisions were: patient age, a medical diagnosis, organ dysfunction,

physician prediction of a low probability of ICU survival, and physician perception of patient preference to limit advanced life-support. This study suggests that there are many dimensions to establishing DNR decisions in the ICU, and highlights the need for clear communication between physicians and surrogate decision-makers about patient preferences for resuscitation prior to, or early in the course of an acute illness. Further research about patients' and surrogates' understanding and expectations of life-support technology, and increasing realistic, sensitive discussions about resuscitation preferences prior to critical illness are imperative to improve end-of-life care.

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