Determinant factors of mortality in terminally ill patients with do-not-resuscitate orders

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Abstract
Background: This study aimed to profile the clinical pictures and identify the risk factors of mortality among terminally ill patients who visited the emergency department (ED) and had signed do-not-resuscitate (DNR) consents.
Methods: This prospective study employed purposeful sampling of 200 adult, non-trauma, terminally ill patients who visited the ED and signed a DNR consent between July 1, 2011, and March 31, 2012. Physiological variables were compared between fatal and survival patients using Student’s t-tests after assessing the normality of the data distribution.
Results: The Cox proportional regression analysis revealed that patients taking antiarrhythmic drugs and vasopressor had a 47.6-fold and 2.8-fold higher mortality, respectively, compared to nonusers and those who had a respiratory rate ≥28 breaths/min showed a 2.8-fold increase in their risk of death compared to those with a respiratory rate <28 breaths/min.
Conclusions: Among terminally ill patients who had signed a DNR consent at the ED, significantly higher hazard ratios of mortality were observed in patients who were on antiarrhythmic drugs or vasopressor, had respiratory rates ≥28 breaths/min, had been intubated, and had serum potassium levels ≥ 4.5 mEq/L.

Keywords: Do-not-resuscitate, mortality, terminally ill patients

INTRODUCTION
Terminally ill patients frequently present to emergency departments (EDs) for symptom control or life prolongation.¹,² The use of aggressive interventions, for example, cardiopulmonary resuscitation (CPR), may be a life-saving intervention for some patients; however, it may be futile in other patients with irreversible clinical progress, leading to unnecessary suffering for the patient and their family.³ According to the relevant provisions of the Palliative Care Act, unnecessary resuscitation should be withheld and withdrawn from terminally ill patients with diseases diagnosed by a physician as incurable with inevitable progress to death in the short term (i.e., survival duration not exceeding 6 months).⁴,⁵ Under such circumstances, physicians in the ED may recommend...
that terminally ill patients or their family members sign a do-not-resuscitate (DNR) consent to avoid unnecessary medical treatment. Some terminally ill patients agree to sign a DNR consent, but others may request invasive treatment for maintenance of vital signs.\(^6\)\(^-\)\(^8\)

The decision to recommend or sign a DNR consent for physicians and terminally ill patients, respectively, is difficult but very important. However, even physicians have not reached a consensus regarding this issue as variable clinical situations such as older age, unstable vital signs, mental confusion, comorbidities, low cardiac output, organ failure, and bedridden condition have been considered for the recommendation of DNR consent.\(^1\)\(^2\)\(^-\)\(^3\) Undoubtedly, the mortality outcome is the most important consideration in the evaluation and the decision to sign a DNR consent.\(^1\)\(^3\) In the clinical setting, DNR may be interpreted by the surrogates in a wide range from “do not perform CPR in the event of cardiac arrest” to “do not treat this patient aggressively if they deteriorate.”\(^1\)\(^4\) As such, no all the patients with a DNR order are going to be fatal. Therefore, the identification of characteristic or physiological indicators associated with mortality of terminally ill patients is necessary to provide a better reference not only for patients who are considering a DNR consent but also for physicians providing care for these patients.\(^1\)\(^5\) Therefore, this study aimed to profile the clinical pictures and identify the risk factors of mortality among terminally ill patients visiting the ED who also signed a DNR consent.

**METHODS**

**Study design and ethics statement**

This was a prospective study that employed purposeful sampling of the characteristics and outcomes of nontrauma adult patients who visited the ED and had signed a DNR consent. This study was preapproved by the Institutional Review Board of the Chang Gung Memorial Hospital (approval number 99-3105B). Informed consent was obtained before conducting interviews and collecting data, and full understanding of the research objective was confirmed. The families were informed during the course of the study, were allowed to ask questions about the study, and could withdraw from the study at any time.

**Study population**

This study was conducted in a 2868-bed medical center in Southern Taiwan that receives approximately 72,000 adult nontrauma ED visits annually.\(^1\)\(^2\)\(^1\)\(^3\) The physicians first assessed probable terminally ill adult patients who visited the ED to evaluate their progressive clinical deterioration and high risk of mortality and to confirm their terminally ill status. The physicians explained the poor condition to the patients’ family members, advising no further aggressive medical interventions, and informed them that hospice care could be provided. After a face-to-face explanation about the purpose of this study to the patient and/or patients’ families and the confirmation of their understanding, DNR consent was obtained and the patients were enrolled in the registry system for data collection and follow-up. The exclusion criteria included patients with out-of-hospital cardiac arrest, patients who committed suicide, whose DNR consents were signed before the study period and had been recorded on their national health insurance cards, those who underwent surgery, and those younger than 18 years of age. Finally, data from 200 patients who had signed a DNR consent were collected between July 1, 2011, and March 31, 2012.

**Study protocol and measurements**

Patient data were extracted from the electronic medical record and ED administrative database. The data collection period started from their arrival at the ED to their deaths or discharge from the hospital, regardless of the length of the hospital stay. These data included sex; age; triage level; vital signs; Glasgow coma scale; laboratory blood test results (e.g., white blood cell count, red blood cell count, hemoglobin, hematocrit, blood urea nitrogen (BUN), serum creatinine, serum sodium, and serum potassium levels); laboratory urine test results; findings of examinations including electrocardiography, echo studies, plain radiological images, computed tomography, or other specific imaging studies; procedures performed in the ED; and underlying diseases (myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, hemiplegia, moderate or severe kidney disease, diabetes, diabetic associated complications, tumor, leukemia/lymphoma, liver disease, malignancy and its metastasis status, and acquired immune deficiency syndrome [AIDS]). The prescribed drugs used to treat the underlying diseases were also recorded. In addition, the Charlson comorbidity index (CCI)\(^1\)\(^4\) scores were also recorded. The CCI predicts 1-year mortality patients with comorbid conditions by summing the weighted value for different conditions such as heart disease, cancer, and AIDS. Two physicians independently reviewed all collected data to identify patient characteristics, clinical diagnoses, and presentations. Inconsistencies between the physicians were resolved following a consensus meeting with a third author.

**Statistical analysis**

The data were compared using IBM SPSS Statistics for Windows, version 18.0 (IBM Corp., Armonk, NY, USA).
The dead and surviving groups of patients were compared. Categorical variables were compared using two-sided Fisher’s exact or Pearson’s Chi-square tests. Continuous variables were expressed as means ± standard deviations and compared using Student’s *t*-test after testing for the normality of the distribution. Cox proportional regression analysis was conducted to identify the continuous or categorical indicators that were significantly predictive of mortality. *P* < 0.05 was considered statistically significant.

**RESULTS**

Profile of the characteristics of the patients who had signed a do-not-resuscitate consent

Among 200 patients who had signed a DNR consent and were enrolled in the current study, 114 (57.0%) and 86 (43.0%) were men and women, respectively [Figure 1]. Their average ages were 72.5 ± 14.9 and 78.3 ± 4.2 years, respectively. There were 81 (40.5%), 52 (26.0%), 28 (14.0%), and 39 (19.5%) patients aged ≥80, 70–79, 60–69, and <60 years, respectively. The most common chief complaint was dyspnea in 85 patients (42.5%), followed by fever and chills in 41 patients (20.5%) and consciousness disturbance in 38 patients (19.0%). The most common underlying disease was cancer in 101 patients (50.5%), followed by organ failure in 48 patients (24%) and cerebrovascular accident (CVA) in 44 patients (22%). Nearly half of the enrolled patients (48%) had a CCI ≥6 points and 80 patients (40.0%) had a CCI between 3 and 5 points. In addition, 99 patients (49.5%) were triaged as Level II upon their arrival to the ED, and 51 (25.5%) and 47 patients (23.7%) were triaged as Level III and Level I, respectively.

Physiological variables of the dead and surviving patients

The average hospital stay among all patients was 14 ± 22 days, with a median of 19 days. A total of 118 patients died and 82 patients survived during their hospital stay [Table 1]. Among the physiological variables analyzed, the patients who died were significant younger (70.8 ± 16.2 vs. 75.0 ± 12.5 years, respectively; *P* = 0.042) and had a lower temperature (36.6°C ± 1.1°C vs. 36.9°C ± 1.0°C, respectively; *P* = 0.018), higher CCI scores (6.1 ± 2.7 vs. 4.8 ± 2.4, respectively; *P* = 0.001), higher potassium levels (4.5 ± 1.2 vs. 4.0 ± 0.7 mEq/L, respectively; *P* < 0.001), higher BUN levels (49.1 ± 42.8 vs. 30.9 ± 27.4 mg/dL, respectively; *P* = 0.002), lower serum bicarbonate (HCO₃⁻) levels (21.9 ± 7.7 vs. 25.7 ± 8.2 mmol/L, respectively; *P* = 0.009), and lower oxygen saturation (91.1% ± 15.9% vs. 98.8% ± 5.5%, respectively; *P* = 0.043) compared to those in the patients who survived.

Predictive risk factors of mortality from Cox proportional regression analysis

As shown in Table 2, the Cox proportional regression analysis revealed that patients using antiarrhythmic drugs had a 47.6-fold higher mortality than those nonusers (hazard ratio [HR] = 47.6, 95% confidence interval [CI] = 5.44–500.00; *P* = 0.001); those using a vasopressor had a 2.8-fold higher mortality than nonusers (HR = 2.8, 95% CI = 1.64–4.81; *P* < 0.001); and those with respiratory rates ≥28 breaths/min had a 2.8-fold increased risk of death compared to those with respiratory rates <28 breaths/min (HR = 2.8, 95% CI = 1.52–5.18; *P* = 0.001). Patients who had been intubated at the ED had
Table 1: Physiological variables of dead and surviving patients who had signed a do-not-resuscitate consent

| Variables                  | Death (n=118) | Survival (n=82) | P   |
|----------------------------|--------------|---------------|-----|
| Age (years)                | 70.8±16.2    | 75.0±12.5     | 0.042* |
| Systolic BP (mmHg)         | 123.3±42.4   | 134.0±43.5    | 0.084 |
| Diastolic BP (mmHg)        | 74.2±25.6    | 79.2±22.1     | 0.154 |
| Respiratory rate (breaths/min) | 22.0±5.3     | 22.5±4.5      | 0.444 |
| Pulse rate (beats/min)     | 99.4±26.3    | 105.6±26.0    | 0.103 |
| Temperature (°C)           | 36.6±11.1    | 36.9±10.1     | 0.018* |
| CCI                        | 6.1±2.7      | 4.8±2.4       | 0.001* |
| WBC (10^3/L)               | 14.9±17.9    | 13.0±7.1      | 0.368 |
| Hemoglobin (g/dL)          | 10.6±2.5     | 10.6±2.3      | 0.993 |
| Hematocrit (%)             | 32.2±7.4     | 31.6±7.5      | 0.526 |
| Platelets (10^3/µL)        | 204.9±128.5  | 216.7±103.4   | 0.491 |
| Sugar (mg/dL)              | 163.8±140.1  | 139.2±70.9    | 0.105 |
| K (mEq/L)                  | 4.5±1.2      | 4.0±0.7       | <0.001 |
| BUN (mg/dL)                | 49.1±42.8    | 30.9±27.4     | 0.002* |
| Creatinine (mg/dL)         | 2.1±2.2      | 1.7±1.9       | 0.219 |
| HCO₃⁻ (mmol/L)             | 21.9±7.2     | 25.7±8.2      | 0.009* |
| Oxygen saturation (%)      | 91.1±15.9    | 98.8±5.5      | 0.043* |

Comparison of physiological variables according to patient outcome. *P<0.05. BP: Blood pressure, CCI: Charlson comorbidity index, WBC: White blood cells, BUN: Blood urea nitrogen, HCO₃⁻: Bicarbonate

Table 2: Significant predictive risk factors of mortality from Cox-proportional regression analysis

| Predictive factors       | Hazard ratio | 95% CI          | P     |
|--------------------------|--------------|-----------------|-------|
| Antiarrhythmic user      | Yes versus no | 47.6            | 5.44-500.00 | 0.001 |
| Vasopressor user         | Yes versus no | 2.8             | 1.64-4.81  | <0.001 |
| Respiratory rate (times/min) | ≥28 versus     | 2.8             | 1.52-5.18  | 0.001 |
| Intubation               | Yes versus no | 2.1             | 1.05-4.12  | 0.035 |
| Potassium level (mEq/L)  | ≥4.5 versus   | 1.6             | 1.33-1.96  | <0.001 |

Cox proportional regression analysis of patients with signed DNR consents. CI: Confidence interval, HR: Hazard ratio, DNR: Do-not-resuscitate

a 2.1-fold increased risk of death relative to nonintubated patients (HR = 2.1, 95% CI = 1.05–4.12; P = 0.035). Finally, patients with hyperkalemia, defined as serum potassium levels exceeding 4.5 mEq/L, had a 1.6-fold increased risk of death compared to patients with normal potassium levels (HR = 1.6, 95% CI = 1.33–1.96; P < 0.001).

**DISCUSSION**

In this study, the patients who died had significantly different physiological variables compared to those of patients who survived, including younger age, lower temperature, higher CCI points, higher potassium and BUN level, and lower HCO₃⁻ and oxygen saturation. The association with older age is in agreement with many studies that reported reduced capacity to recover following cardiac arrest in the elderly because of lower functional reserves and higher prevalence of comorbidities.[13] Hypothermia, defined as a temperature ≤35°C, is common in critically ill patients and is one of the most important physiological predictors for early and late mortality.[14] In critically ill patients, the complexity of the temperature curve is inversely related to the patient’s clinical status.[17,18] However, the mean temperature of the patients who died in the current study was 36.6°C, which does not meet the definition of hypothermia; further, the difference in temperature between the patients who died and survived was <0.5°C (36.6°C ± 1.1°C vs. 36.9°C ± 1.0°C, respectively; P = 0.018), indicating that this physiological variable is less useful for the identification of patients at high risk for mortality. The CCI is the most commonly used comorbidity index and has good predictive power for increased mortality compared with other scales.[19-22] The CCI independently predicts short- and long-term mortality in acutely ill hospitalized elderly adults[23] and showed good-to-excellent discrimination regarding predictions of in-hospital mortality.[19,22]

Mild abnormalities in serum potassium levels have also been suggested as a marker of disease as severe hyperkalemia is a potentially life-threatening electrolyte imbalance and frequently attributed to cardiac dysfunction and increased mortality in critically ill patients.[24] Despite appropriate and aggressive treatment, the rate of in-hospital mortality among patients with severe hyperkalemia was around 30%. Azotemia due to dehydration and acute renal failure are frequently observed in terminally ill cancer patients.[25] BUN is a significant factor of mortality and has been used as a marker for malnutrition or cachexia, a physical sign of impending death. Multivariate analysis showed that BUN, in addition to hypotension and serum levels of C-reactive protein and sodium, was an independent factor of 1-week and 1-month mortality.[24] Patients with BUN levels >40 mg/dL had a higher risk of mortality relative to patients with BUN levels of 10–20 mg/dL.[27] The HCO₃⁻ levels are strongly correlated with arterial base deficit/excess, and they provide equivalent predictive information for metabolic acidosis and mortality in critically ill patients.[28] Bicarbonate levels have been associated with mortality of patients admitted to the Intensive Care Unit after in-hospital CPR.[29]

The results of this study revealed a significantly higher HR for mortality among patients who had signed a DNR when these patients had used antiarrhythmic drugs or vasopressor, had respiratory rates ≥28 breaths/min, had been intubated, and had high serum potassium levels (≥4.5 mEq/L). In critically ill patients, acute heart failure is frequent and leads to mortality due to arrhythmias, cardiac dysfunction, and myocardial injury.[30] Vasopressors, including pure vasoconstrictors (phenylephrine and vasopressin) and inoconstrictors (dopamine, norepinephrine, and...
epinephrine), increase the mean arterial pressure by augmenting vascular tone and are usually used to relieve the symptoms of tissue hypoperfusion.\(^{31}\) Arrhythmia and hypotension are critical conditions that reflect hemodynamic changes and may be life-threatening if not aggressively treated.\(^{32}\) Unsurprisingly, the use of antiarrhythmic drugs or vasopressors is associated with increased mortality among terminally ill patients. However, the effect and the status of discontinuing vasopressor use on mortality are unknown in this study and thus may lead to a bias in identifying the mortality risk and the use of vasopressor. In addition, dyspnea or tachypnea is a significant prognostic indicator of mortality in critically ill patients.\(^{33}\) This is also the most common symptom experienced by dying patients and patients with advanced cancer.\(^{34}\) The incidence of dyspnea increases significantly 1–3 months before death.\(^{35}\) Therefore, the observation in this study, that is, patients who were intubated for a ventilation support had a higher risk of mortality than nonintubated patients, was expected.

Various physiologic and laboratory parameters were associated with mortality in patients who had signed a DNR consent. However, it is not easy to accurately anticipate the grave prognosis of terminally ill patients because the physiological indices measured in the ED are usually affected by abrupt changes in the patient's condition.\(^{36}\) This may be particularly true for variables such as oxygen saturation, respiratory rate, and serum levels of potassium, BUN, and bicarbonate. These indices may have improved or deteriorated after administration of certain types of immediate management in the ED before a DNR consent was signed and patients were enrolled in the current study, which would result in a major limitation in the interpretation of the results. In this study, there was an average hospital stay of 14 ± 22 days, with a median of 19 days, among all patients. Although a longer hospital stay was important factor affecting the surrogates’ decision-making to sign a DNR,\(^{37}\) the long hospital stay of these patients with DNR orders may also indicate the importance of early implementation of palliative care, which has been shown to improve the quality of care and resource utilization for inpatients,\(^{38,39}\) to the patients. This study also has several other limitations. First, the nonrandomized sampling resulted in a bias in the baseline covariates used for comparison. Second, the recommendation of a DNR consent by the physicians without standards or guidelines could result in a selection bias. In addition, because there were no established protocols for the management of patients who had signed a DNR consent, we could only assume the uniform management of the enrolled patients by different physicians during the treatment course.

Third, terminally ill patients with advanced diseases other than cancer tend to have a more uncertain prognosis.\(^{40}\) and the long-term mortality of these patients was not evaluated in this study. Finally, aside from mortality, certain important indicators were not evaluated from different perspectives, such as the socioeconomic, psychological, and administrative viewpoints.

**CONCLUSION**

In this study, we observed a significantly higher HR for mortality among patients who had signed a DNR consent who had used anti-arrhythmic drugs or vasopressor, had a respiratory rate ≥28 breaths/min, had been intubated, and had high serum potassium levels (≥4.5 mEq/L).

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**Conflicts of interest**

There are no conflicts of interest.

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