ORIGINAL RESEARCH

Early and late do-not-resuscitate (DNR) decisions in patients with terminal COPD: a retrospective study in the last year of life

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Purpose: The unpredictable trajectory of COPD can present challenges for patients when faced with a decision regarding a do-not-resuscitate (DNR) directive. The current retrospective analysis was conducted to investigate factors associated with an early DNR decision (prior to last hospital admission) and differences in care patterns between patients who made DNR directives early vs late.

Patients and methods: Electronic health records (EHR) were reviewed from 271 patients with terminal COPD who died in a teaching hospital in Taiwan. Clinical parameters, patterns of DNR decisions, and medical utilization were obtained. Those patients who had a DNR directive earlier than their last (terminal) admission were defined as "Early DNR" (EDNR).

Results: A total of 234 (86.3%) patients died with a DNR directive, however only 30% were EDNR. EDNR was associated with increased age (OR=1.07; 95% CI: 1.02–1.12), increased ER visits (OR=1.22; 95% CI: 1.10–1.37), rapid decline in lung function (OR=3.42; 95% CI: 1.12–10.48), resting heart rate ≥100 (OR=3.02; 95% CI: 1.07–8.51), and right-sided heart failure (OR=2.38; 95% CI: 1.10–5.19). The median time period from a DNR directive to death was 68.5 days in EDNR patients and 5 days in "Late DNR" (LDNR) patients, respectively ($P<0.001$). EDNR patients died less frequently in the intensive care unit ($P<0.001$), received less frequent mechanical ventilation (MV; $P<0.001$), more frequent non-invasive MV ($P=0.006$), and had a shorter length of hospital stay ($P=0.001$).

Conclusions: Most patients with terminal COPD had DNR directives, however only 30% of DNR decisions were made prior to their last (terminal) hospital admission. Further research using these predictive factors obtained from EHR systems is warranted in order to better understand the relationship between the timing associated with DNR directive decision making in patients with terminal COPD.

Keywords: do-not-resuscitate, electronic health record, medical utilization, share decision making

Introduction

COPD is a chronic illness that presents as a chronic productive cough and progressive shortness of breath.[1] COPD was the seventh leading cause of death in Taiwan in 2015 and estimates suggest it will be the third leading cause of death worldwide in 2030.[2,3] Patients with advanced COPD often have a poor prognosis[4]; however, advanced COPD patients receive intensive care more frequently compared with patients diagnosed with lung cancer.[5–9] Patients with advanced COPD have increased comorbidities, spend more days in the hospital, have more invasive

procedures, are more likely to die in the intensive care unit (ICU) and are less likely to have a do-not-resuscitate (DNR) directive.[10–13]

Cardiopulmonary resuscitation (CPR) performed in patients with a terminal illness is often ineffective and is associated with a reduction in quality of end-of-life care.[14] A DNR directive indicates a patient's refusal to accept CPR when suffering from cardiac or respiratory arrest and is one of the most commonly discussed advance directives in palliative care.[15,16]

In 2000, the Hospice Palliative Care Act (HPCA) became a law in Taiwan, with amendments following in 2002, 2012, and 2013.[17,18] People who suffer from a terminal illness, when certified by two physicians, have the right to refuse CPR.[18] According to the HPCA, a DNR directive can be made in one of two ways: signed by a competent terminally ill patient (DNR will) or by a close relative (DNR consent) when the patient is no longer capable of making that decision for himself/herself.[19]

Other international guidelines have emphasized the importance of advance care directives being made early in patients with late stage COPD[1,20]; however, several barriers have been identified. COPD has an unpredictable disease trajectory.[21,22] It is difficult to predict the death of a patient with COPD within six months.[23,24] Common parameters for prognostic criteria include measures of lung function, degree of hypoxia, history of hospitalization, and recent ventilator support – all of which have been found to be unreliable.[25–28] Therefore, the timing of decisions regarding DNR directives in most patients with COPD may occur closer to death than not, and that decision may not be made by the patient themselves.

The aim of this study was to investigate factors associated with an early DNR decision (prior to last [terminal] hospital admission) and differences in care patterns between patients who made DNR directives early vs late. The timing of DNR decisions, who made the DNR decision, and the medical utilization of patients with COPD who died in a medical center in Taiwan were analyzed. Factors associated with early DNR decisions as obtained from hospital electronic health records (EHR) were also analyzed to provide additional insight for physicians, patients and their families to support their decision making when faced with a decision regarding a DNR directive.

Methods

Consecutive patients whose primary or secondary cause of death was COPD (based on ICD, ninth revision, Clinical Modification [ICD-9-CM] coding) between 2011 and 2015, and whose death occurred in Taichung Veterans General Hospital (TCVGH), Taiwan, were included in this retrospective observational cohort study. Subjects with fewer than two TCVGH visits for the management of the symptoms associated with their COPD in the last year of life were excluded. TCVGH is a tertiary teaching hospital and the only public medical center located in central Taiwan. Patient demographics, diagnostic test results, treatment history, including palliative care, at TCVGH, was collected using the EHR system. The study protocol was fully reviewed and approved by the Institutional Review Board of the Taichung Veterans General Hospital (TCVGH-IRB) Taiwan (IRB number: CE17017A, date of approval: 11/22/2016). The requirement for informed patient consent was waived by the TCVGH internal review board considering the retrospective study design and the availability of all data via electronic medical records. Only de-identified patient data was used in this study.

Study population

EHRs from a total of 271 patients were included in the analysis. Eligible patients were ≥40 years of age, had been diagnosed with COPD (ICD-9-CM codes 491.x, 492.x, and 496.x), had been admitted to the hospital for acute care, and died in the hospital between June 1, 2011 and December 31, 2015. Patients who met the inclusion criteria but were discharged in critical condition or terminal status were also included in the analysis.

Operational definitions of outcome measures

All subjects were validated according to the official criteria for "terminal status in COPD."[29] Terminal status in COPD refers to having symptoms of dyspnea at rest, a progressive condition, and any of the following conditions: 1) Respiratory insufficiency (with or without oxygen support [$PaO_2 \leq 55$ mmHg, $PaCO_2 \geq 50$ mmHg, or O_2 saturation ≤88%]); 2) $FEV_1 \leq 30\%$ of predicted; 3) FEV_1 declined ≥40 mL/year; 4) Weight loss ≥10% in 6 months; 5) Resting heart rate ≥100/min; 6) Right-sided heart failure; and 7) Multiple comorbidities: (eg, cachexia, recurrent infection, depression, or multiple comorbidities).[8,9]

Patients with COPD or their surrogates who had a DNR directive prior to their last (terminal) admission to the hospital were classified as Early DNR (EDNR). Whereas, Late DNR (LDNR) patients were those who implemented a DNR directive during their last admission.

Assessment

We collected data on patient age, gender, pulmonary function test results (FEV$_1$/FVC ratio and FEV$_1$%), heart function (two-dimensional echocardiography), medical utilization (number of emergency room (ER) visits and hospitalizations), and any CPR (cardiac pulmonary resuscitation) within 1 year prior to death. Additional information obtained during the last (terminal) hospital admission included whether admitted from the ER, died on the service of a pulmonologist, died in the ICU, or experienced mechanical ventilation (such as invasive and non-invasive mechanical ventilation). The frequency of each criterion met by each patient with COPD was calculated. Furthermore, timing of a signed DNR directive and the patient status (terminal or not terminal) was also recorded. The total number of days from each patient's signed DNR consent until their deaths, as well as the number of days from physician confirmed terminal status to patient death were analyzed.

Statistical analysis

Statistical analyses were completed using SPSS version 22.0 (International Business Machines Corp, Armonk, NY, USA). For nonparametric distribution data, differences between groups were assessed using a Mann–Whitney U test and results were presented as median and interquartile range (IQR). The categorical variables were presented as frequency and percentage and analyzed using the chi-squared test. Factors associated with EDNR were assessed using univariate analysis and those with significant difference were assessed using multivariate analysis. The strength of association was presented as the odds ratio (OR) and 95% confidence intervals (CI). All results with $P<0.05$ were deemed to be statistically significant.

Results

Characteristics of COPD deaths

A total of 271 deaths due to COPD fit the enrollment criteria. Patient characteristics and the study flow chart are summarized in Table 1 and Figure 1. Patients with COPD who died in the hospital were aged, predominately male, and experienced frequent ER visits and hospitalizations. Most patients (94.5%) were admitted from the ER on their last (terminal) admission to the hospital, 59.8% of patients died while being treated by a pulmonologist, and 32.5% died in the ICU. Despite 86.3% of patients having a DNR directive, 83.0% still experienced mechanical ventilation (MV) and 67.5% experienced invasive MV. Only 11.1% had been

Table 1 Demographic characteristics of patients with COPD who died in a medical center over a period of 5 years (2011–2015) (N=271)
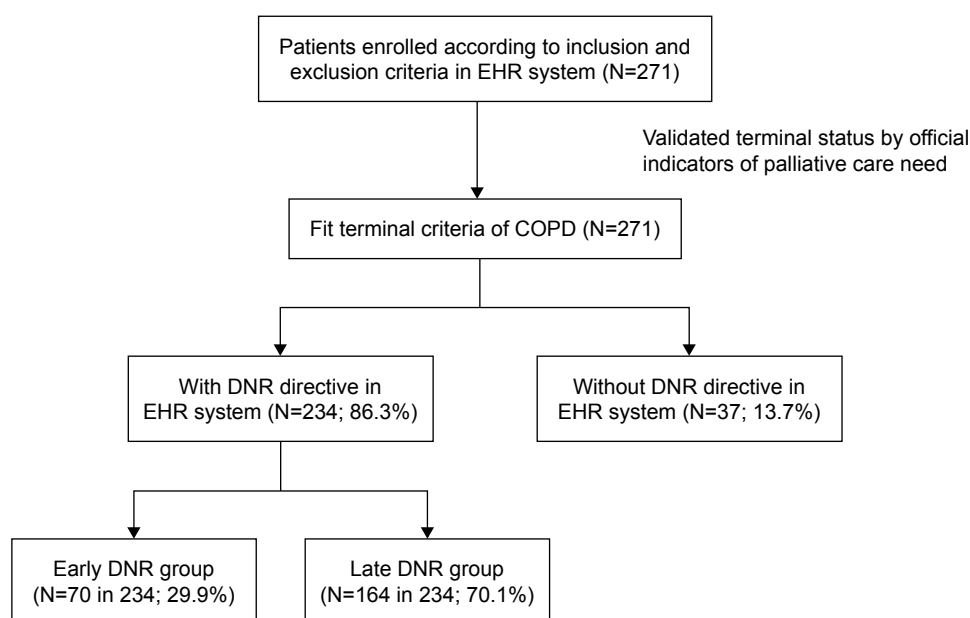
Characteristics	Data
Age (Median, IQR)	83 (77–88)
Male	249 (91.9%)
Pulmonary function test within 1 year prior to death (Median, IQR) (n=96)	
FEV$_1$/FVC%	48.5 (39–62)
FEV$_1$%	60.5 (40–81.8)
Medical utilization within 1 year prior to death (Median, IQR)	
Number of ER visits	2 (1–3)
Number of hospitalizations	1 (1–3)
Experienced CPR	18 (6.6%)
Medical utilization in the last admission	
Admitted from ER	256 (94.5%)
Died on the service of a pulmonologist	162 (59.8%)
Died in the ICU	88 (32.5%)
Experienced mechanical ventilation	225 (83.0%)
Had only Invasive MV	119 (43.9%)
Had only NIPPV	106 (39.1%)
Ever had both MV and NIPPV	64 (23.6%)
Extubated with NIPPV support	136 (50.2%)
Clinical indicators for palliative care (Median, IQR)	4 (3–5)
Patient wishes recorded (DNR)	234 (86.3%)
DNR in the last admission prior to death	164 (70.1%)
DNR within 30 days prior to death	175 (74.8%)
Time period from DNR request to death (Median, IQR)	8.5 (3–32)
Terminal status certified by a physician	30 (11.1%)
Terminal status certificated in the last admission (n=30)	24 (80.0%)

Abbreviations: DNR, do-not-resuscitate; ER, emergency room; FEV$_1$, forced expiration volume in the first second of expiration; FVC, forced vital capacity; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilator; NIPPV, non-invasive positive pressure ventilator.

documented as being terminal by the attending physician, and almost 80% of these were documented during the last admission when the patient was near death. Although 86.3% of patients had expressed an interest in establishing a DNR directive by themselves or via their family surrogates, greater than 70% of the DNR directives were made during the last admission prior to death.

Validated official criteria for "terminal status in COPD"

Since only 11.1% of COPD deaths were documented as terminal status near death, the terminal condition according to the official criteria required validation.[29,30] In our retrospective analysis, all patients fit the official criteria for "terminal status in COPD."[29] The top three criteria were respiratory insufficiency (94.1%), multiple comorbidities (89.7%), and resting heart rate greater than 100 bpm (78.2%; Table 2).

Figure 1 Study flow chart.
Notes: "Early DNR" was defined as "COPD patients or their surrogates who had DNR directive prior to their last admission." "Late DNR" was defined as "COPD patients or their surrogates who had DNR directive during their last admission."
Abbreviations: DNR, do-not-resuscitate; EHR, Electronic health records.

"Early DNR," "Late DNR," and patterns of care during the last admission for COPD

EDNR patients were aged, had more frequent ER visits and hospitalizations, and met the criteria for "terminal status" more frequently than LDNR patients (all $P<0.05$; Table 3). The EDNR group had an increased frequency of rapid declines in lung function ($P=0.014$), resting heart rate ≥100 bpm ($P=0.024$) and right-sided heart failure ($P=0.003$). EDNR patients died less frequently in the ICU ($P<0.001$), used less invasive mechanical ventilation (MV) ($P<0.001$), used non-invasive MV more frequently ($P=0.006$) and had

Table 2 The official indicators of "terminal status in COPD" in Taiwan

Criteria	Fit cases (n, %)
1) Respiratory insufficiency (even with oxygen support, $PaO_2 \leq55$ mmHg, $PaCO_2 \geq50$ mmHg or O_2 saturation $\leq88\%$)	255 (94.1%)
2) $FEV_1 \leq30\%$ of predicted	44 (16.2%)
3) FEV_1 declined ≥40 mL/year	72 (26.6%)
4) Weight loss $\geq10\%$ in 6 months	106 (39.1%)
5) Resting heart rate ≥100/min	212 (78.2%)
6) Right-sided heart failure	116 (42.8%)
7) Multiple comorbidities: (eg, cachexia, recurrent infection, depression, or multiple comorbidities)	243 (89.7%)

Note: "Terminal status in COPD": for COPD patients who suffered from breathlessness even when resting, and the condition continued to deteriorate (such as: repeated ER visits or hospitalizations due to pneumonia or respiratory failure), combined with any of the above conditions.
Abbreviation: FEV_1, forced expiration volume in the first second of expiration.

shorter lengths of stay before death ($P=0.001$). The amount of time between DNR request to death was also significantly longer in the EDNR group compared with the LDNR group (median: 68.5 days and 5 days, respectively, $P<0.001$; Table 3 and Figure 2).

Factors associated with EDNR

Factors associated with EDNR are shown in Table 4. Using a univariate analysis, older age (odds ratio; OR=1.08; 95% CI: 1.04–1.13, $P<0.001$), frequent ER visits (OR=1.25; 95% CI: 1.13–1.38, $P<0.001$), meeting more clinical indicators for palliative care (OR=1.32; 95% CI: 1.09–1.60, $P=0.005$), rapid decline in pulmonary function (OR=2.23; 95% CI: 1.22–4.10, $P=0.009$), resting heart rate ≥100 bpm (OR=2.56; 95% CI: 1.18–5.59, $P=0.018$), and right-sided heart failure (OR=2.49; 95% CI: 1.40–4.42, $P=0.002$) were associated with EDNR. "Terminal status documented by a physician" was not correlated with an early DNR directive (OR=1.97; 95% CI: 0.90–4.32, $P=0.09$). Multivariate analysis was applied to those factors found to be significant with univariate analysis. The multivariate analysis showed that older age (OR=1.07; 95% CI: 1.02–1.12, $P=0.005$), frequent ER visits (OR=1.22; 95% CI: 1.10–1.37, $P<0.001$), rapid decline in pulmonary function (OR=3.42; 95% CI: 1.12–10.48, $P=0.031$), resting heart rate ≥100 bpm (OR=3.02; 95% CI: 1.07–8.51, $P=0.036$), and right-sided heart failure (OR=2.38; 95% CI: 1.10–5.19, $P=0.028$) were significantly

Table 3 Comparison of care pattern and terminal criteria between "Early DNR" and "Late DNR"

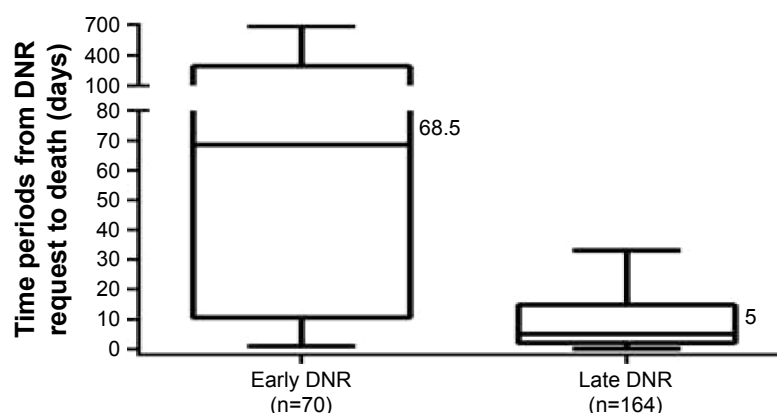| Characteristics	Early DNR (N=70)	Late DNR (N=164)	P-value
Age (Median, IQR)	87 (83–90)	82 (75–85.75)	<0.001**
Male	62 (88.6%)	154 (93.9%)	0.257
Lung function test within 1 year prior to death (Median, IQR) (n=24 vs 56ᵃ)			
FEV$_1$%	51.5 (38.3–77.3)	59 (38.5–81.8)	0.785
Medical utilization within 1 year prior to death (Median, IQR)			
Number of ER visits	3 (2–6)	1 (1–3)	<0.001**
Number of hospitalizations	2 (1–4)	1 (1–2)	<0.001**
Experienced CPR	2 (2.9%)	4 (2.4%)	1.000
Terminal status recorded by physicians	13 (18.6%)	17 (10.4%)	0.132
Numbers of clinical indicators met for terminal status	4 (3–5)	3 (3–4.75)	0.001**
Items that meet the official indicator of terminal status:			
1) Respiratory insufficiency (even with oxygen support, PaO$_2$ ≤55 mmHg, PaCO$_2$ ≥50 mmHg or O$_2$ saturation ≤88%)	66 (94.3%)	156 (95.1%)	0.755
2) FEV$_1$ ≤30% of predicted	16 (22.9%)	24 (14.6%)	0.180
3) FEV$_1$ declined ≥40 mL/year	27 (38.6%)	36 (22.0%)	0.014*
4) Weight loss ≥10% in 6 months	26 (37.1%)	68 (41.5%)	0.637
5) Resting heart beats ≥100/min	61 (87.1%)	119 (72.6%)	0.024*
6) Right side heart failure	43 (61.4%)	64 (39.0%)	0.003**
7) Multiple comorbidities: (eg, cachexia, recurrent infection, depression or multiple comorbidities)	65 (92.9%)	147 (89.6%)	0.597
Time periods from making DNR directives to death	68.5 (10.5–292.8)	5 (2–14.8)	<0.001**
Medical utilization in the last admission			
Admitted from ERᵃ	68 (97.1%)	153 (93.3%)	0.354
Died on the service of a pulmonologist	44 (62.9%)	97 (59.1%)	0.700
Died in the ICU	5 (7.1%)	65 (39.6%)	<0.001**
Experienced mechanical ventilator	48 (68.6%)	145 (88.4%)	0.001**
Only using invasive MV	8 (11.4%)	85 (51.8%)	<0.001**
Only using NIPPV	40 (57.1%)	60 (36.6%)	0.006**
Extubated with NIPPV support	39 (55.7%)	89 (54.3%)	0.952
Length of stay in the last admission	11.5 (4.0–21.0)	19.0 (10.0–34.8)	<0.001**

Notes: Mann–Whitney U test. Chi-squared test. ᵃFisher's exact test; *P<0.05, **P<0.01. ᵃNot everyone has lung function data in their last year.
Abbreviations: CPR, cardio-pulmonary resuscitation; DNR, do not resuscitate; ER, emergency room; FEV$_1$, forced expiration volume in the first second of expiration; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilator; NIPPV, Non-invasive positive pressure ventilator.

associated with early DNR requests. However, when using a multivariate analysis, age remained a significant factor and numbers of clinical indicators was not a significant factor (OR=0.68; 95% CI: 0.44–1.06, P=0.091).

Discussion

Three major findings were demonstrated in the current study. First, the official criteria for "terminal status in COPD" was validated – all enrolled COPD patients (N=271) fit the official

Figure 2 Period of time from DNR directive to death between "Early DNR" and "Late DNR" groups in terminal patients with COPD.
Notes: Median: 68.5 days and 5 days, respectively, P<0.001.
Abbreviation: DNR, do not resuscitate.

Table 4 Factors associated with EDNR

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.08	(1.04–1.13)	<0.001**	1.07	(1.02–1.12)	0.005**
Male	0.50	(0.19–1.33)	0.168			
Lung function test within 1 year prior to death						
FEV$_1$%	1.00	(0.98–1.01)	0.688			
Medical utilization within 1 year prior to death						
Number of ER visits	1.25	(1.13–1.38)	<0.001**	1.22	(1.10–1.37)	<0.001**
Number of hospitalizations	1.11	(0.98–1.26)	0.093			
Number of clinical indicators met for terminal status	1.32	(1.09–1.60)	0.005**	0.68	(0.44–1.06)	0.091
Experienced CPR	1.18	(0.21–6.58)	0.853			
Terminal status certificated by physicians	1.97	(0.90–4.32)	0.090			
Terminal criteria						
1) Respiratory insufficiency (even with oxygen support, PaO$_2$ ≤55 mmHg, PaCO$_2$ ≥50 mmHg or O$_2$ saturation ≤88%)	0.85	(0.25–2.91)	0.791			
2) FEV$_1$ ≤30% of predicted	1.73	(0.85–3.50)	0.129			
3) FEV$_1$ declined ≥40 mL/year	2.23	(1.22–4.10)	0.009**	3.42	(1.12–10.48)	0.031*
4) Weight loss ≥10% in 6 months	0.83	(0.47–1.48)	0.537			
5) Resting heart beats ≥100/min	2.56	(1.18–5.59)	0.018*	3.02	(1.07–8.51)	0.036*
6) Right side heart failure	2.49	(1.40–4.42)	0.002**	2.38	(1.10–5.19)	0.028*
7) Multiple comorbidities: (eg, cachexia, recurrent infection, depression or multiple comorbidities)	1.50	(0.53–4.25)	0.442			

Notes: Logistic regression. *P<0.05, **P<0.01.
Abbreviations: CPR, cardio-pulmonary resuscitation; EDNR, early do-not-resuscitate; ER, emergency room; FEV$_1$, forced expiration volume in the first second of expiration.

criteria for terminal COPD. To the best of our knowledge, this is the first research to validate the official criteria for "terminal COPD" using real-world data from Taiwan.

Second, a gap of DNR decisions and the identification of terminal COPD status between patients/their surrogates and physicians was observed. In this cohort, 234 of the 271 patients with COPD (86.3%) had signed a DNR directive before they died; however, only 30 of the 271 patients with COPD (11.1%) had been confirmed and documented as being terminal status by physicians. Of the 234 cases with a DNR order, 233 cases were from family surrogates and only one patient made their own decision. According to the "Hospice Palliative Care Act" in Taiwan, two scenarios are possible when making a decision regarding a DNR directive.[17,18] 1) It could be made by a patient themselves (DNR signed by patient), or 2) by their surrogate (DNR signed by surrogate).[19] In this case it is possible the physicians had initiated conversations with family surrogates prior to last admission. Previous studies in Taiwan suggested patients who understand the prognosis of their disease or have previous discussions about a DNR order tend to have a DNR directive, however, in a real-world setting a family surrogate often needs to make a DNR directive on behalf of patients who cannot express their intention at end of life.[16] In a local survey of 201 nursing home residents in Taiwan, the result showed that 16.4% had DNR directives, and 91% of these DNR directives were signed by family surrogates.[31] This situation is the same as

reports from Europe and North America that older patients prefer to make their final DNR directives by themselves.[32,33] The current data not only reflect the unmet need for early advance care planning in COPD even when the "Hospice Palliative Care Act" is taken into account, but also show the uncertainty of physicians in identifying terminal status in patients with COPD. This phenomenon may contribute to the important barriers, such as poor communication between patients and physicians and the unpredictable trajectory of COPD when initiating DNR decisions.[34–36] Third, we have identified factors associated with executing a DNR early by patients and/or their surrogates. EDNR patients had less intensive care, died less frequently in the ICU, and had shorter lengths of stay in the hospital in the last admission before they died when compared with the LDNR group. These results suggest that obtaining an early DNR directive (by patients or their surrogates) changed the attitude and treatment strategy of physicians. Only 11% of terminal patients with COPD were documented as in terminal status by physicians.

It is difficult to predict the death of patients with COPD within 6 months.[22–24] Although pulmonary function tests (PFT) were important indicators of the prognosis for COPD,[12,35] in the current study, only 35.4% (96 of 271 patients) had a PFT within 1 year prior to death. Heart failure is one of the most common comorbid conditions in COPD.[37,38] The presence of pulmonary hypertension and right-sided heart failure doubles the mortality in patients with COPD.[39,40] In our data, severe COPD

accompanied by documented right-sided heart failure was significantly associated with early DNR directives (OR=2.49; 95% CI: 1.40–4.42). We suggest that an annual follow-up PFT and heart function surveys are important in helping physicians to evaluate the disease progression of COPD.

There are some limitations to this study. First, the retrospective design collected data in a hospital. Therefore, it was possible to have missed patients due to inappropriate ICD-9-CM coding, underreporting, and/or incorrect electronic medical records diagnoses. Second, the care continuity of these COPD patients would be challenged for the missing data of medical utilizations. Since we have excluded subjects with fewer than two physician visits for COPD in TCVGH in their last year of life and the most critical COPD patients will be referred to TCVGH in central Taiwan, we could lower the impact of these two limitations. Third, we could not obtain the view point of patients and their surrogates due to the limitations of the study design. Fourth, the uncertainty of a clear definition of COPD terminal status would be a limitation for physicians expected to certify this status for their patients with COPD within an electronic medical record. Fifth, the results were based on a single medical center, so they may not represent the situation in other places or countries.

Conclusion

In this study, we currently report that despite 86.3% of patients with terminal COPD having DNR directives, only 11.1% had their terminal status documented by a physician, and 70% of DNR directives were made in the last admission before death. The major decision makers for the DNR directives were not the patients themselves, rather family surrogates. The time gap between "Early DNR" and "Late DNR" was nearly 60 days before death. By using information from EHRs, "Early DNR" was associated with older age, more ER visits, rapid decline in lung function, tachycardia and right-sided heart failure. Further research to routinely capture these predictive factors in existing EHR databases to help patients, their surrogates, and primary care physicians to share decision making in advanced COPD is warranted in the future.

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Author contributions

The authors listed in the article meet conditions as following: Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafting

the article or revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors report no conflicts of interest in this work.

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