ORIGINAL RESEARCH

Dynamic Changes in Prognosis with Elapsed Time on Ventilators among Mechanically Ventilated Patients

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Abstract

Rationale: Previous outcome studies of mechanical ventilation usually adopted a static timeframe to observe the outcome and reported prognosis from the standpoint of the first ventilator day. However, patients and their families may repeatedly inquire about prognosis over time after the initiation of mechanical ventilation.

Objectives: We aimed to describe dynamic changes in prognosis according to the elapsed time on a ventilator among mechanically ventilated patients.

Methods: For this cohort study we used the entire population dataset of Taiwan's National Health Insurance database. We enrolled adults who newly received invasive mechanical ventilation for at least two consecutive days between March 1, 2010, and August 31, 2011. For every single ventilator day after the initiation of mechanical ventilation, we estimated the cumulative probabilities of weaning success and death in the subsequent 90 days.

Results: A total of 162,200 episodes of respiratory failure requiring invasive mechanical ventilation were included. The median age of the subjects was 72 years (interquartile range 57–81 yr) and the median follow-up time was 250 days (interquartile range 30–463 d). The probability curve of weaning success against the time on ventilation showed a unidirectionally decreasing trend, with a relatively sharp slope in the initial 2 months. The probabilities of weaning success in 90 days after the 2nd, 7th, 21st, and 60th ventilator days were 68.3% (95% confidence interval [CI], 68.1–68.5%), 62.6% (95% CI, 62.2–62.9%), 46.3% (95% CI, 45.8–46.8%), and 21.0% (95% CI, 20.3–21.8%), respectively. In contrast, the death curve showed an initial increase and then a decreasing trend after the 19th ventilator day. We also reported tailored prognosis information according to the age, sex, and ventilator day of a mechanically ventilated patient.

Conclusions: This study provides ventilator-day–specific prognosis information obtained from a large cohort of unselected patients on invasive mechanical ventilation. The probability of weaning success decreased with the elapsed time on mechanical ventilation, and the decline was particularly remarkable in the first 2 months of ventilatory support.

Keywords: mechanical ventilation; outcome; prognosis; respiratory failure; weaning

As the population ages and the burden of comorbidities increases worldwide, the use of mechanical ventilation is growing (1, 2). The availability of updated and patient-specific information about the clinical course and outcome of respiratory failure requiring mechanical ventilation is important for patient care, shared decision-making, research, and healthcare policymaking (3–6). Previous outcome studies of mechanical ventilation usually adopted a static timeframe to observe outcomes and reported prognosis from the standpoint of the first ventilator day (7, 8). However, patients and their family members may repeatedly inquire about prognosis over time after the initiation of mechanical ventilation. Therefore, information that can capture dynamic changes in prognosis over time may facilitate physician–patient communication, especially when the duration of ventilator use is prolonged (9, 10).

We conducted a large-scale cohort study to address this important issue. For this study we used Taiwan's National Health Insurance (NHI) database, which continuously and precisely records the history of mechanical ventilation use and survival status for every patient. Using the NHI data, we estimated the subsequent 90-day probabilities of weaning success and death for every single ventilator day.

Methods

Study Design and Setting

This study was part of a governmental project with respect to its investigation of the use of mechanical ventilation in Taiwan. This nationwide cohort study used the entire population database, which contains information about the daily medical care use and death status of each enrollee in Taiwan's NHI (11). The Taiwan NHI is a universal and compulsory health insurance program that includes more than 99% of its citizens (11). Taiwan's National Health Insurance Administration maintains the quality of the NHI data by conducting routine audits. In 2000, the Taiwan NHI initiated a payment program to encourage integrated care for mechanically ventilated patients. This program universally pays for the medical cost of mechanical ventilation with no constraints on the total duration of ventilation. To reduce inappropriate use of invasive-care facilities, the National Health

Insurance Administration has put substantial effort into building relevant datasets for program management, and auditing the quality of mechanical ventilation care. This background furnished a well-equipped research database for our study.

The study was approved by the Institutional Review Board of National Health Research Institutes, Taiwan (EC1051202-E-R1). Because all individual identification numbers in our research database were encrypted to protect the privacy of the study participants, informed consent was waived.

We used a database that links Taiwan NHI data and other individual data. The Taiwanese government specifies that researchers can only analyze such data in a room where the government stores the database, after their requests for access have been approved. In this case, no individual data can be brought outside the room, and researchers can only bring away statistical results based on the data. Currently, applications of this type have to be sent to the Ministry of Health and Welfare, Taiwan. Interested parties may send requests for data to stcarolwu@mohw.gov.tw. In either case, institutional review board approval and payment for use of the data are required.

During the study period, Taiwan's medical community did not practice the terminal withdrawal of ventilator support owing to concerns regarding Taiwanese family culture and medical disputes. The model of care provided to mechanically ventilated patients under the regulation of the Taiwan NHI is addressed in the online supplement.

Establishment of the Study Cohort

This study focused on patients who had been placed on mechanical ventilation for at least 2 days. Referring to the NHI medical order code for invasive mechanical ventilation, we identified patients who newly received invasive mechanical ventilation for at least two consecutive days between March 1, 2010 and August 31, 2011 (Figure E1 in the online supplement). The selection of the study period was based on the availability of data when we submitted our proposal to the Taiwanese government. Our investigation included only patients who were adults (≥18 years old) when mechanical ventilation was initiated. The data allowed us to observe each patient from the day of mechanical ventilation initiation until

death, disenrollment from the NHI, or the end of April 2012, whichever occurred first. Disenrollment from Taiwan's NHI only occurs when a beneficiary loses his or her Taiwan citizenship, moves overseas, or is missing for at least 6 months. Details regarding the patients and hospitals included in the study are provided in the online supplement.

Statistical Analysis

We used SAS software version 9.4 (SAS Institute Inc.) to extract the NHI data, construct the data matrices for the survival analysis, and describe research variables. We used Stata software version 14 (StataCorp) to conduct the survival analysis. We reported the point estimate of each prognosis indicator, as well as the corresponding 95% confidence interval (CI). Weaning success was defined as a period of five consecutive ventilator-free days, as in our previous study (12).

We adopted a postestimation calculation based on results from the Kaplan-Meier estimator. We used the Kaplan-Meier estimator to generate a life table that reported the number of patients still at risk (those who remained alive and dependent on invasive mechanical ventilation for respiratory support) and the number of events (for subjects who were weaned from invasive mechanical ventilation and subsequently survived at least 5 d) on each day after t_0.

To calculate the cumulative probability of weaning success for the ith ventilator day, we first summed up the numbers of weaning success events for the ith ventilator day and the subsequent 89 days. Next, we divided the total number of events by the number of patients still at risk on the ith ventilator day (those who remained alive and dependent on invasive mechanical ventilation for respiratory support on the ith day, and might be censored for death before the end of follow-up). For comparative purposes, we also estimated a model based on the competing-risk regression model to further generate the cumulative incidence curve of weaning success since the beginning of the second ventilator day. The model treated death as the competing risk. We used the bootstrap method to assess the precision of the point estimates from the competing-risk regression. The results of this analysis are shown in Figures E2 and E3.

Similarly, we estimated the probability of death for the ith ventilator day. We

summed up the numbers of death events for the ith ventilator day and the subsequent 89 days, and then divided the total number of death events by the number of patients still at risk on the ith ventilator day.

We performed a subgroup analysis to evaluate the probabilities of weaning success and death in common subgroups of patients receiving mechanical ventilation. Specifically, we conducted analyses separately for different groups based on age (<70 yr vs. ≥70 yr), presence of pneumonia, admission type (medical vs. surgical), and existence of obstructive airway disease. The definitions of these subgroups are provided in the online supplement.

Results

Patient Characteristics

The study included a total of 162,200 episodes of invasive mechanical ventilation for at least two consecutive days. The median follow-up time was 250 days (interquartile range [IQR] 30–463 d). The median age of the study cohort was 72 years (IQR 57–81 yr), and 59,164 episodes (36.5%) occurred in women. The median duration of ventilator use was 7 days (IQR 3–17 d) and 33,926 episodes (21%) lasted for more than 21 days. Table 1 summarizes the baseline characteristics of the study population. Table E1 provides information about important cointerventions for the 162,200 episodes of mechanical ventilation.

Prognosis Observed at the Initiation of Mechanical Ventilation

To depict the clinical course of mechanical ventilation, we selected each patient's first episode of mechanical ventilation from the 162,200 episodes. This process identified a total of 136,656 patients for the analysis. Figure 1 presents the 90-day clinical course observed after the initiation of mechanical ventilation. As shown in Figure 1, weaning success was achieved in 68.8% of the patients, 28.6% died without achieving weaning success, and 2.7% continuously depended on mechanical ventilation care. Among those patients who achieved weaning success, 77.1% remained ventilator free at the end of the 90-day period and 9.2% required repeat intubation.

Figure 2A demonstrates the cumulative probabilities of death and weaning success, showing the change in probability over time based on observations after the initiation of

Table 1. Baseline characteristics of the study cohort (162,200 episodes of mechanical ventilation)

Characteristic	No. of episodes (%)
Age in years, median (interquartile range)	72 (57–81)
18–24	2,469 (1.5)
25–34	6,145 (3.8)
35–44	9,456 (5.8)
45–54	18,170 (11.2)
55–64	24,595 (15.2)
65–74	31,822 (19.6)
75–84	46,208 (28.5)
85+	23,335 (14.4)
Female sex	59,164 (36.5)
Reason for initiation of mechanical ventilation	
Medical (without any operation)	104,710 (64.6)
Postoperative	57,490 (35.4)
Preexisting comorbidity before mechanical ventilation	
Heart failure	3,638 (2.2)
Renal failure requiring renal replacement therapy	8,243 (5.1)
Obstructive airway disease	23,234 (14.3)
Liver cirrhosis	2,046 (1.3)
Stroke	6,672 (4.1)
Diabetes	35,444 (21.9)
Malignancy	24,515 (15.1)
Hematological cancer	1,136 (0.7)
Solid cancer	23,379 (14.4)
Hospital level of the index hospitalization	
Medical center	66,903 (41.3)
Regional hospital	72,834 (44.9)
District hospital	22,463 (13.8)
Urbanization	
Big city	62,595 (38.6)
Small city or town	61,731 (38.1)
Rural area	37,874 (23.4)

mechanical ventilation. The cumulative probability at a time point refers to the probability of the outcome event during the time period from the beginning of follow-up to that time point. Figure 2B shows the cumulative frequency of weaning success in 180 days. More than 90% of successful weaning happened in the initial 30 days.

Prognosis Evaluated on Each Ventilator Day

Figure 3 presents curves depicting the subsequent 90-day probabilities of weaning success and death on each ventilator day after the initiation of mechanical ventilation. For each ventilator day, the initial time for follow-up was the beginning of that day. The probabilities of weaning success estimated for the 7th, 21st, and 60th ventilator days were 62.6% (95% CI, 62.2–62.9%), 46.3% (95% CI, 45.8–46.8%), and 21.0% (95% CI, 20.3–21.8%), respectively. The curve of weaning success plotted against the ventilator day showed a unidirectionally

decreasing trend, with a relatively sharp slope in the first 2 months. In contrast, the death curve showed an initial increase and then a decreasing trend after the 19th ventilator day. On the 28th ventilator day, the probability of death started to exceed the probability of weaning success, and this relationship remained thereafter.

Figure 4 shows the results of subgroup analyses for the 90-day probabilities of weaning success and death according to age (<70 vs. ≥70 yr), presence of pneumonia (yes or no), admission types (medical or surgical), and existence of obstructive airway disease (yes or no). The relationships between ventilator days and subsequent probabilities of weaning success or death were similar across the subgroups, but the point estimate of the outcome measures differed modestly from that observed for the total cohort. Table E3 lists the point estimates of the probabilities of weaning success and death for the total cohort and selected subgroups.
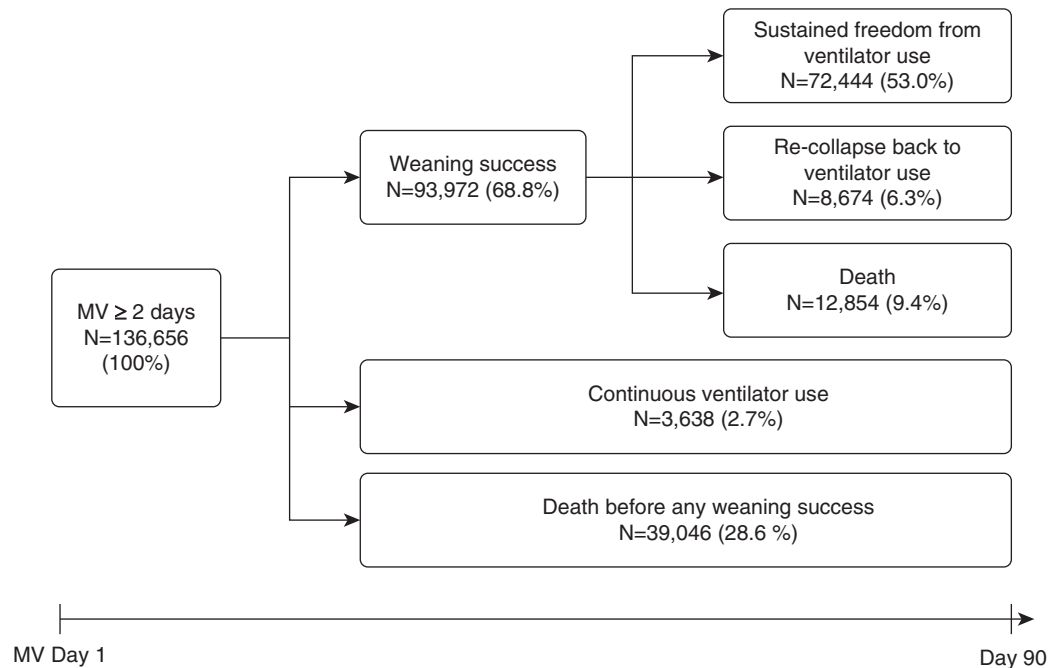
Figure 1. Clinical course of patients who received mechanical ventilation (MV) care for at least 2 days.

Discussion

Our study depicts the clinical course and ventilator-day–specific prognosis of respiratory failure requiring invasive mechanical ventilation in a large sample of unselected patients. The probability curve of weaning success against the time on ventilation showed a unidirectionally decreasing trend, with a relatively sharp slope in the initial 2 months. In contrast, the death curve showed a nonmonotonic direction, with an initial increase and then a decreasing trend after 3 weeks. Our analysis was based on nonparametric methods, which have the advantage of having only minimal requirements for statistical assumptions. We demonstrate how researchers can use big data in a healthcare system to investigate dynamic changes in prognosis that occur in critically ill patients. Mechanically ventilated patients may require various forms of assistance and support from their family members depending on the duration of ventilator use and the probabilities of successful liberation and death in the near future. Patients and their families might benefit from receiving conditional daily prognosis information to help with treatment choices, visitation, and work-leave planning (13, 14).

To increase the convenience of using data generated by this study, we set up an online inquiry system (http://mvp.nhri.org.tw/NHIA-NHRI2017/count.html) to report tailored prognosis information corresponding to various ventilator-day, age, and sex strata. The probability values reported in this inquiry system were based on the method that was used to generate Figure 3. By referring to these data, persons involved in discussions about prognosis and care plans for patients with a critical illness can get a clearer picture of how to respond to changes in the future path of prognosis. The critical care community recommends that a shared decision-making model for care planning should incorporate multiple discussion sessions involving the intensive care unit team and patient surrogates (15). However, reaching a consensus in family meetings about the prognosis of mechanically ventilated patients may require solid prognosis data. Previous studies showed a gap between patients' expectations and actual outcomes (9). Because our inquiry system contains quantitative information about prognosis, it can be used by healthcare personnel to facilitate communication with patients and their surrogates. The age-, sex-, and ventilator-day–specific data from a large, real-world practice database could

give a patient a sense of the prognosis of patients in similar situations.

In this study we did not particularly stress the disease-specific outcomes of mechanical ventilation. Rather, we focused on reporting the prognosis data stratified by ventilator day and patient demographics. The duration of mechanical ventilation may be a proxy indicator reflecting the excess of respiratory demand relative to capacity. The approach used in this study provides an alternative way to understand a prognosis of respiratory failure, and has advantages over traditional disease-oriented approaches when the causes of respiratory failure are multifactorial or complex. The disease-specific outcomes reported in previous studies were usually confined to single etiology–related respiratory failure (16, 17), and may have limited generalizability to patients with multiple comorbidities. Furthermore, data on the conditional probability of weaning success by ventilator day (Figure 3) provide more insight into dynamic changes in prognosis than a traditional time-to-event analysis from a specific day in the initial stage of ventilator use (Figure 2A).

The results of the subgroup analysis shown in Figure 4 and Table E3 suggest that the relationships between ventilator days and probabilities of weaning success or
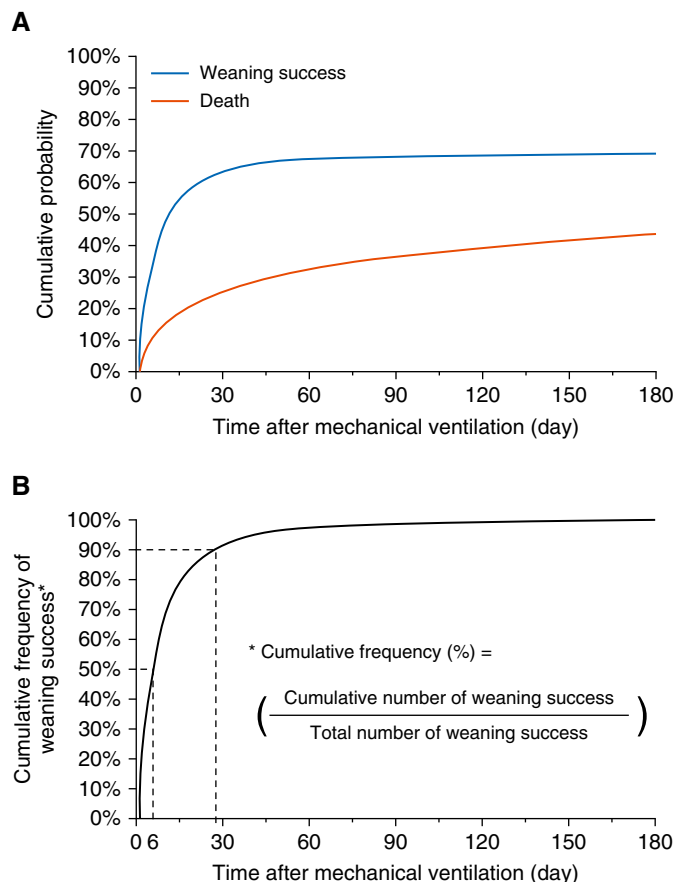
A

B

Figure 2. (*A*) Probability curves of death and weaning success for patients who received at least 2 days of mechanical ventilation care. Cumulative probability refers to the probability of the outcome event during the time period. (*B*) The curve of the cumulative frequency of weaning success shows the proportion of weaning success before a specified time point.

death are similar across subgroups, but the point estimate of the outcome measures in each subgroup differs modestly from that of the total cohort. The extent of deviation depends on the prespecified conditions. For example, patients <70 years of age had better weaning outcomes than the total cohort, but the differences in the probability
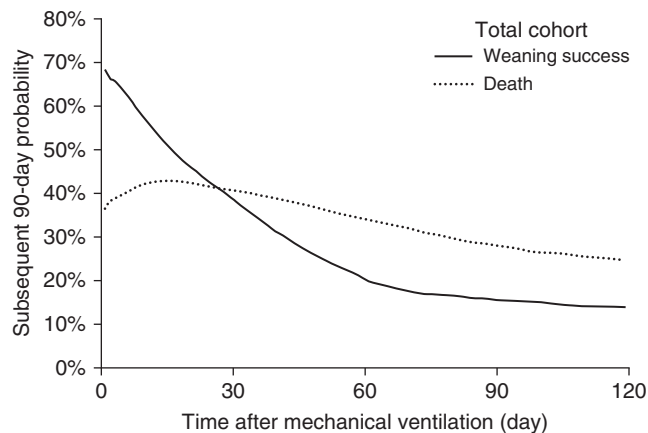

Figure 3. Curves depicting the subsequent 90-day probabilities of weaning success and death on each ventilator day after the initiation of mechanical ventilation. For each ventilator day, the follow-up started at the beginning of that day.

of weaning success were <10% at each time point; in contrast, the differences between the surgical and total cohorts were relatively larger than the difference between the other subgroups and the total cohort. Comparisons of surgical and medical patients showed that the surgical patients were much younger, had fewer comorbidities, and were more likely to be treated in the medical center than the medical patients (Table E2). This might explain why surgical patients were associated with a better weaning outcome.

An operational classification for the weaning process based on the number, timing, and results of spontaneous breathing trials (SBTs) has been proposed (18). Epidemiology and weaning outcomes according to this new classification were prospectively evaluated in a multinational study termed WIND (Weaning according to a New Definition) (19). In the WIND study, ventilated patients were categorized into three groups: simple weaning, difficult weaning, and prolonged weaning. Prognosis was evaluated and reported according to these three categories. No further information was provided about a difference in prognosis within the same category. For instance, prolonged weaning was defined as a condition in which a patient is unable to be liberated from mechanical ventilation after more than three SBTs or >7 days from the first SBT. However, the prognosis may differ between prolonged weaning for 8 days versus 28 days. The WIND classification system is a simple approach for prognosis stratification but has limitations in providing a detailed prognosis for prolonged-weaning patients. Our approach provides a ventilator-day–specific prognosis after intubation, which is valuable for clinicians and patients who may want to know more specific information beyond that provided by the category-based approach.

Our study also furnishes new information about prolonged mechanical ventilation (PMV). The common definition of PMV is a status of continuous ventilator use for at least 21 days (6). Although the rationale for this discrimination is ambiguous, the notion of PMV has greatly affected healthcare policy and resource allocation (20–22). Correspondingly, a consensus guideline called for more studies to investigate the prognostic property of ventilator days in ventilated patients (6). As shown in Figures 2 and 3, the 21st ventilator day is not associated with particular
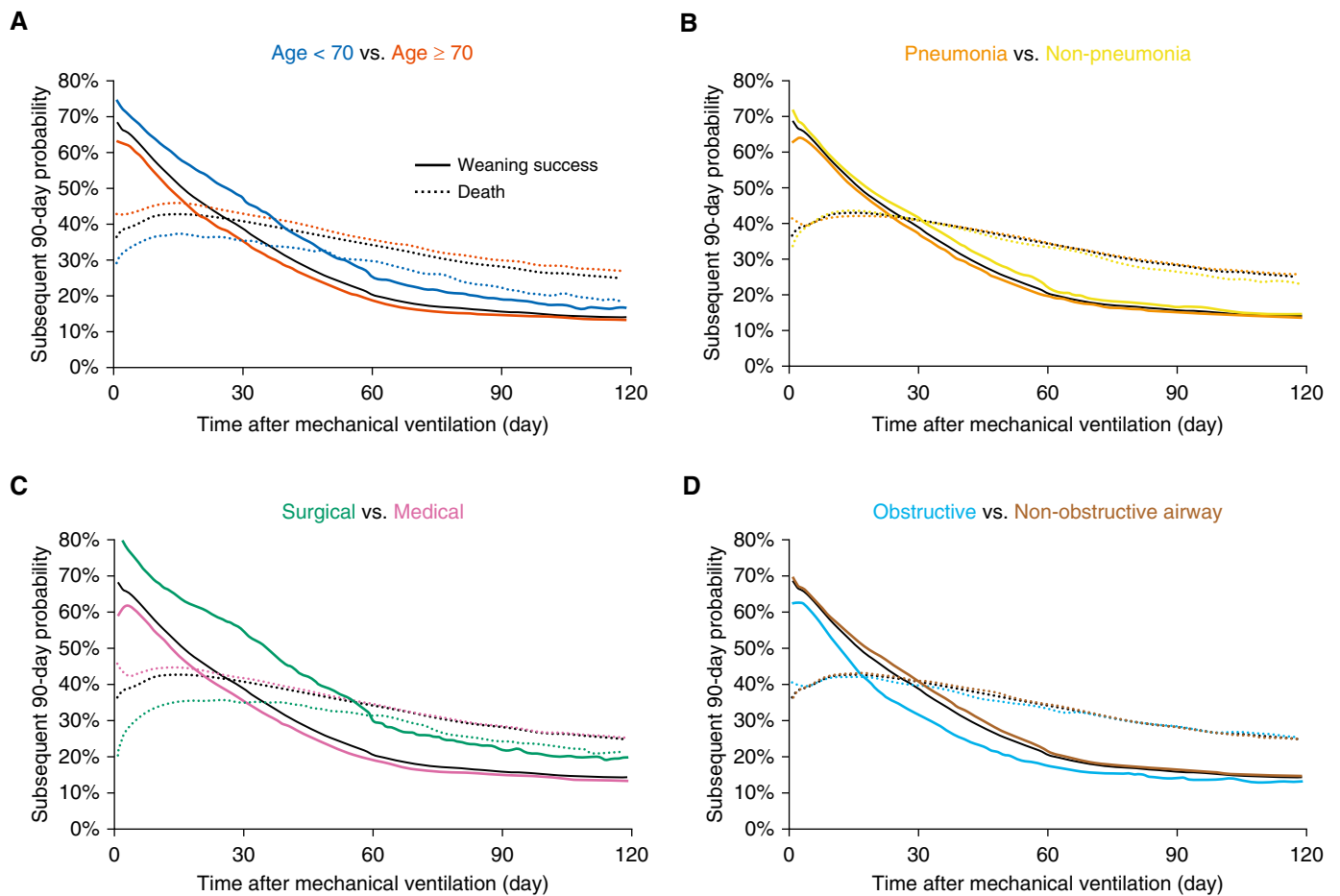
Figure 4. Curves showing the results of a subgroup analysis of the 90-day probabilities of weaning success and death over time. The solid lines denote the probabilities of weaning success and the dotted lines denote the probabilities of death. The black lines are the reference lines from the total cohort. (*A*) Patients <70 years old (blue lines) versus patients ≥70 years old (red lines). (*B*) Patients with pneumonia (orange lines) versus those without pneumonia (yellow lines). (*C*) Surgical (green lines) versus medical (purple lines) patients. (*D*) Patients with obstructive airway disease (blue lines) versus those without obstructive airway disease (brown lines).

prognostic relevance. In contrast, the probability curve of weaning success has a plateau after Day 30 (Figure 2A), which indicates that ventilator dependence for more than 30 days would enter a steady state with low weaning potential. Figure 2B demonstrates that >90% of successful weaning occurred in the initial 30 days. After Day 30, <10% of weaning success occurred during the subsequent 150 days. These data suggest that if the definition of PMV aims to identify a subgroup of mechanically ventilated patients linked to poor weaning outcomes, a cutoff of 30 ventilator days may be a reasonable choice. Compared with the curve of weaning success, the probability curve of death shows a continuously increasing trend without any plateau phase. Prolonged ventilator use is associated with an increased risk of

mortality resulting from ventilator-induced lung injury and other complications (23). Without focusing on the duration of mechanical ventilation, the syndrome of chronic critical illness is an updated concept to identify patients who survive an initial critical condition but continue to suffer from organ dysfunction and remain in an inflammatory state for a long period of time (24). The concept of chronic critical illness was not intended to strictly determine a threshold of ventilator days for its definition criteria.

Palliative withdrawal of ventilator support was not practiced in Taiwan during the study period. Palliative withdrawal may change the clinical course of respiratory failure requiring mechanical ventilation. If palliative withdrawal is allowed, the duration of ventilator use is shortened and

death occurs earlier than it would without withdrawal. The effect on the results of our analysis would be that the probabilities of death increase during the early days of ventilation but decrease during the later days of ventilation. The magnitude of the influence of palliative withdrawal on the prognosis curves depends on the proportion of palliative withdrawals in the total mechanical ventilation episodes. In addition to mortality, palliative withdrawals also influence the probability curve of weaning success. The patients who received palliative withdrawal were usually those with a low weaning potential. The effect of palliative withdrawals may result in an increase in the probability of weaning success for the remaining ventilated patients.

Our study has a few limitations. First, it was a single-country study whose results

reflect the context of clinical practice regarding mechanical ventilation in Taiwan. Accordingly, external generalizability of the results is a potential concern. One should consider the patient characteristics and care models for mechanically ventilated patients before applying the prognosis data presented here. Second, our prognosis data represent the outcome of the average patient without comprehensively considering underlying diseases. Thus, the data are less informative when the underlying diseases have decisive effects on outcomes, such as in the case of motor neuron disease. Third, we had no information about individual patients' do-not-resuscitate orders, which makes it difficult to determine whether the timing of the patients' deaths reflects biological mechanisms or patient and family decision-making. Finally, we adopted a strict criterion for the diagnosis of comorbidities; therefore, the prevalence of comorbidities in ventilated patients may be underestimated in this study.

Conclusions

In this study we used a large database to describe dynamic changes in prognosis with elapsed time on ventilators among mechanically ventilated patients, and report age-, sex-, and ventilator-day–specific prognosis data. The information about the dynamic changes in prognosis on mechanical ventilation may facilitate efficient physician–family communication regarding outcomes when the duration of ventilator use is prolonged. This study also provides an example of using big data in the healthcare system to improve the reporting of prognosis data for critically ill patients. ■

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