The Effect of Clusters of Double Triggering and Ineffective Efforts in Critically Ill Patients

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ABSTRACT

OBJECTIVES: To characterize clusters of double triggering and ineffective inspiratory efforts throughout mechanical ventilation and investigate their associations with mortality and duration of ICU stay and mechanical ventilation. **DESIGN:** Registry-based, real-world study. **BACKGROUND:** Asynchronies during invasive mechanical ventilation can occur as isolated events or in clusters and might be related to clinical outcomes. **SUBJECTS:** Adults requiring mechanical ventilation greater than 24 hours for whom greater than or equal to 70% of ventilator waveforms were available. **INTERVENTIONS:** We identified clusters of double triggering and ineffective inspiratory efforts and determined their power and duration. We used Fine-Gray's competing risk model to analyze their effects on mortality and generalized linear models to analyze their effects on duration of mechanical ventilation and ICU stay. **MEASUREMENTS AND MAIN RESULTS:** We analyzed 58,625,796 breaths from 180 patients. All patients had clusters (mean/d, 8.2 [5.4–10.6]; mean power, 54.5 [29.6–111.4]; mean duration, 20.3 min [12.2–34.9 min]). Clusters were less frequent during the first 48 hours (5.5 [2.5–10] vs 7.6 [4.4–9.9] in the remaining period [$p = 0.027$]). Total number of clusters/d was positively associated with the probability of being discharged alive considering the total period of mechanical ventilation ($p = 0.001$). Power and duration were similar in the two periods. Power was associated with the probability of being discharged dead ($p = 0.03$), longer mechanical ventilation ($p < 0.001$), and longer ICU stay ($p = 0.035$); cluster duration was associated with longer ICU stay ($p = 0.027$). **CONCLUSIONS:** Clusters of double triggering and ineffective inspiratory efforts are common. Although higher numbers of clusters might indicate better chances of survival, clusters with greater power and duration indicate a risk of worse clinical outcomes.

KEY WORDS: clusters; competing risk; double triggering; ineffective inspiratory efforts; patient-ventilator interactions

INTRODUCTION

Asynchronies during invasive mechanical ventilation (MV) reflect a mismatch between ventilator cycles and patients' respiratory demands (1, 2). Asynchronies are common throughout MV and are associated with prolonged MV and ICU stay, discomfort, dyspnea, sleep disruption, respiratory muscle dysfunction and lung injury, and increased mortality (3–12); however, asynchronies can also signal clinical improvement (13).

Breath-by-breath analysis of patient-ventilator interaction allows the computation of an asynchrony index; values greater than 10% are considered high (4, 14, 15). However, the index provides no details about patterns of occurrence. Clustered asynchronies could affect physiologic variables and clinical outcomes more than isolated asynchronies; the impact might depend on the number of asynchronies within a cluster (power) and/or on the duration of the cluster. Vaporidi et al (16) found that the power and duration of clusters of ineffective inspiratory efforts were associated with prolonged MV and increased hospital mortality. Clusters of other asynchronies and/or combinations of asynchronies might also have physiologic and clinical consequences (17).

Competing risk analysis is an approach to survival analysis required in situations with multiple possible events where the occurrence of one event precludes or substantially modifies the possibilities of other events from developing (18–20). Status at ICU discharge comprises two mutually exclusive possibilities: dead or alive. Standard survival analysis disregards the possibility of differing profiles for the events "discharged alive" and "discharged dead" and may overestimate the risk of mortality (21–24).

We hypothesized that clusters of double triggering and ineffective inspiratory efforts would affect out-comes. We aimed to detect and characterize clusters of these asynchronies throughout MV, to investigate the association between clusters and status at ICU discharge, and to analyze whether the power and duration of clusters influences duration of MV and ICU stay.

MATERIAL AND METHODS

Patients and Data

This registry-based cohort study used data from a prospectively constructed database of noncoronavirus disease ICU patients (ClinicalTrials.gov NCT03451461). Intubated adults were continuously monitored at bedside with the BC Link platform (Better Care SL, Barcelona, Spain) (25–27) (for details, see online data supplement). Exclusion criteria were age less than 18 years, MV less than 24 hours, pregnancy, do-not-resuscitate orders, chest tubes with suspected bronchopleural fistula, and admission for organ donation. Additionally, to ensure data quality, we excluded patients for whom less than 70% MV waveforms from the total period on MV were available. All patients were managed following the Spanish Society of Intensive Care Medicine's quality indicators (https://semicyuc.org/wp-content/uploads/2018/10/indicado-resdecalidad2017_semicyuc_spa-1.pdf).

Detection and Characterization of Clusters of Asynchronies

This study considered only double triggering and ineffective inspiratory efforts (see online data supplement for definitions and detection algorithm). The cluster-detection algorithm was based on the mathematical description by Vaporidi et al (16) of clusters of ineffective inspiratory efforts. However, because other types of asynchronies can have lower (26) or higher incidences than ineffective inspiratory efforts and may be more harmful than ineffective efforts, we used a lower threshold to define a cluster: a period in which greater than 10% of the total number of respiratory cycles contained double triggering and/ or ineffective efforts (e.g., > 6 asynchrony events in a 3-min period, assuming a respiratory rate of 20 breaths/ min). Starting and ending points were set at 80% of the maximum value of the smoothed time series (Fig. 1). We characterized each cluster in terms of its power (i.e., number of events in the cluster) and duration (length of time in minutes) (for details, see online data supplement).

Data Analysis

The primary clinical endpoint was status at ICU discharge (dead or alive). Secondary endpoints were duration of MV and ICU stay. Independent variables were the number of clusters and their mean power and duration.

We analyzed the data from the entire period of MV. We also separately analyzed the data from two periods: the first 48 hours' MV (to study clusters' consequences during the most acute phase of critical illness) and the remaining time receiving MV. We excluded from the analysis periods in which recording was interrupted due to clinical interventions, out-of-ICU transfers, technical problems, or other issues.

Statistical Analysis

No sample size was calculated for this exploratory study.

Data are summarized as medians (25–75th percentiles) or as percentages when appropriate. To compare variables between the two periods, we used the Wilcoxon signed-rank test. To model patients' status at ICU discharge, we used Fine-Gray's competing-risk model (18, 22, 23). We used generalized linear models to investigate possible associations between power and duration of clusters and duration of MV and ICU stay. To control potential bias resulting from varying length of MV among patients, the total number of clusters was corrected for the number of days on MV in each period. All models were adjusted for age and Acute Physiology and Chronic Health Evaluation (APACHE) II. Furthermore, we considered the combined effect of power and duration by including their interaction (for details, see online data supplement). We used R 3.6.1 (R Core Team, Vienna, Austria) for all analyses, considering p value less than 0.05 significant.

Ethical Approval and Consent to Participate

The Comitè d'Ètica d'Investigació at the Corporació Sanitària Parc Taulí and the Clinical Research Ethics Committee of Fundació Unió Catalana d'Hospitals approved the database

and the study protocol (Approval number: 2011/619). Informed consent was waived because the study was noninterventional, added no risk to patients, did not interfere with usual care, and used anonymized data. Spanish regulations were followed (Biomedical Research Law 14/2007).

RESULTS

We screened 400 consecutive patients from four centers, excluding 220 patients without high-quality waveforms for greater than or equal to 70% of the total time receiving MV; thus, we report data from 180 patients at two centers (median time receiving MV, 8 d [4–14.2 d]; median missing recordings, 22.5 hr [13.5–57.25 hr]) who spent a total of 46,683.5 hours on MV comprising 58,625,796 breaths. Table 1 reports demographic, clinical, and outcome data for the patients included.

Clusters: Characteristics, Distribution, and Neuromuscular Blockade

All patients had clusters of asynchronies during MV (median number of clusters/d on MV, 8.2 [5.4–10.6]; mean power, 54.8 [29.6–111.4] asynchrony events; mean duration, 20.4 min [12.3–35 min]). Figure 2 illustrates the distribution of cluster-related variables during the entire time receiving MV, during the first 48 hours of MV, and during the remaining period of MV. The total number of clusters/d on MV was lower during the first 48 hours than in the remaining time under MV (5.5 [2.5–10] vs 7.6 [4.4–9.9]; $p = 0.027$). The two periods did not differ in the mean power (36.4 [18.4–98.1] vs 43.4 [26.7–97.1] events; $p = 0.993$) or mean duration (15.9 min [7.1–29.6 min] vs 17.6 min [10.6–31.1 min]; $p = 0.679$) of clusters.

Due to the difficulty of accessing older medical records in paper format, information on neuromuscular blockade use could only be obtained for 98 patients. Briefly, 11 (11.2%) received Neuromuscular blockade at some point during the first 48 hours, and only two of them during the first and second day of MV. For details, see online data supplement.

Status at ICU Discharge (Dead or Alive)

In the univariate analysis, total number of clusters/d while receiving MV, mean power, and mean duration were associated with the probabilities of being dead or alive at ICU discharge (Supplementary Table 1 and Fig. E1). In the multivariate analysis adjusting for age and APACHE II and adding the interaction between the mean power and mean duration of clusters (Table 2), total number of clusters/d was negatively associated with the risk of death, both when the total period of MV was considered ($p < 0.001$) and when each of the two time periods were analyzed separately ($p = 0.001$ in the first 48 hr and $p < 0.001$ in the remaining period). Total number of clusters/d during the total period of MV was positively associated with the probability of being discharged alive ($p = 0.001$), as was total number of clusters/d during the first 48 hours ($p < 0.001$). Mean power of clusters during the total period of MV was positively associated with the probability of being dead at discharge ($p = 0.03$), as was the mean power of clusters during the first 48 hours ($p < 0.001$), which was also negatively associated with being discharged alive ($p < 0.005$). Mean duration was strongly correlated with mean power (Spearman correlation coefficient = 0.89).

The interaction between mean power and mean duration was associated with the probability of being dead or alive at discharge in analyses of the first 48 hours and of the total period of MV (for details, see online data supplement), a simulated clinical case illustrating the findings, and separate multivariate analyses of clusters of ineffective efforts (Supplementary Table 3) and double triggering (Supplementary Table 4).

Duration of MV and ICU Stay

In the univariate analysis, the number, power, and duration of clusters were associated with the duration of MV and ICU stay (Supplementary Table 2). In the multivariate regression model (Table 3) adjusting for age and severity and adding the interaction between the mean power and mean duration of clusters, the number of clusters/d was not associated with the duration of MV ($p = 0.152$) or ICU stay ($p = 0.113$) when the whole period of MV was

considered. Mean power of clusters was positively associated with the duration of MV ($p < 0.001$) and ICU stay ($p = 0.035$) in the whole period and in the period starting after the first 48 hours ($p < 0.001$ for MV and $p = 0.018$ for ICU stay). By contrast, mean duration of clusters was positively associated only with ICU length of stay in all three periods (whole period, $p = 0.027$; first 48 hr, $p = 0.018$; remaining time on MV, $p = 0.037$) (for additional details, see online data supplement).

DISCUSSION

All patients developed clusters of asynchronies, suggesting clusters are common. Remarkably, the total number of clusters was associated with increased probability of being alive at ICU discharge. Importantly, however, the power and duration of clusters were associated with longer duration of MV and ICU stay and increased probability of death, mainly during the first 48 hours of MV. Thus, clusters of asynchronies are potentially more harmful than isolated asynchronies and their detection should alert clinicians to the need for caution.

Using a prototype monitor to automatically detect ineffective inspiratory efforts in 24-hour recordings obtained on the first, third, and sixth day of MV, one study found clusters in 38% of patients, and clusters were associated with hospital mortality and increased length of MV (16). Another study using a twice daily visual analysis protocol found asynchronies in 30% of patients and were associated with higher mortality (28). Another study that used automatic-detection software to analyze the entire period of MV in 103 patients found clusters of double triggering in 87% of them, and these clusters were associated with worse survival and longer MV and ICU stay (17). To avoid underestimating the effect of clusters, we chose the lowest threshold that was significant for mortality to define a cluster (10%); this percentage is considerably lower than in the study by Vaporidi et al (50%) (16).

In our study, clusters were less frequent during the first 48 hours of MV. This difference might be related to increased severity and/or greater use of sedation and paralysis during the most

acute phase of illness; nevertheless, the duration and power of clusters were similar in the two periods. Interestingly, clusters developed in both of the two most common modes, assist-controlled and pressure-support ventilation.

Clusters' Effects on Duration of MV, ICU Stay, and Mortality

The power and duration of clusters were similar in the first 48 hours and in the remaining period of MV, but power was associated with an increased probability of death only in clusters occurring during the first 48 hours. These observations could have various hypothetical explanations. The physiologic consequences of clusters could include diaphragmatic injury (29, 30), elevated transpulmonary pressure swing (31), high tidal volumes and breath stacking (26, 32), occult pendelluft effect (33, 34), and elevated stress and strain in dependent lung. All these phenomena could aggravate previous lung injuries, so a second-hit hypothesis could explain the observed effect of the power of clusters (35–37). The impact of clusters with a given power is likely to increase with their duration; furthermore, these two variables are strongly correlated, so very short clusters are unlikely to have high power.

Our results extend the knowledge gained from three recent studies (16, 17, 28). Vaporidi et al (16) studied 110 patients and 2,931 hours of MV with, an automatic system to detect clusters of ineffective efforts during the first 24 hours after switching patients to pressure-support ventilation or proportional modes but stopped recording if patients returned on controlled modes. They found that clusters of ineffective efforts were associated with higher hospital mortality and longer duration of MV. In another study in 120 patients, See et al (28) visually examined monitor tracings for 2 minutes every 12 hours to detect asynchronies; they found that the observance of asynchronies on more than one occasion (i.e., recurrence) was associated with increased mortality. Analyzing the entire period of MV, Sousa et al (17) found that patients with a high cumulative duration of clusters of double triggering had fewer ventilator-free days, longer duration of MV, longer ICU stay, and shorter survival than patients with low cumulative duration.

Unlike the first two of those studies (16, 28), we used validated software capable of identifying and quantifying asynchronies in real time together with a robust statistical approach to analyze the effects of clusters of the two most common asynchronies (26, 32) on outcomes. This approach found that a higher number of clusters during the entire period of MV was associated with a higher probability of being alive at ICU discharge, and this association was also valid for each of the two periods studied. These results are in line with those reported by Rué et al (13), where a competing-risk analysis of the longitudinal trajectory of the asynchrony index measured daily found that the greater the asynchrony index, the greater the probability of being discharged alive. Importantly, the asynchrony index only reflects the number of asynchronies, disregarding whether they appear in clusters. Moreover, another recent study showed that the asynchrony index predicted extubation failure, but not mortality (38).

Focusing on clusters of asynchronies rather than on isolated events may give a more accurate picture of how asynchronies are distributed (9, 16). Our findings suggest clinicians should aim to detect and prevent high-power clusters to avoid possible harmful effects, especially during the first 48 hours. Furthermore, our results suggest that efforts to build artificial intelligence– assisted ventilator-management systems should incorporate automatic cluster detection and characterization.

Our results corroborate that the power of clusters of some type of asynchronies is associated with longer MV and ICU stays, whereas duration was associated only with longer ICU stay (4, 6, 16, 28), shedding light on the importance of the power and duration of clusters in the observed effects on these two outcomes.

However, identifying clusters can prompt various clinical actions that could have detrimental effects, such as increasing sedation. Thus, further research is needed to establish the optimal balance between risks and benefits of treatments to manage asynchronies. Finally, to explain the relationship between asynchronies in the first 48 hours of MV and status at ICU discharge,

the interaction term between power and duration was necessary, making the combined effect of both more important than these elements considered separately.

Limitations

Our study has potentially significant limitations such as availability of waveforms and quality of data. Some eligible patients were excluded due to missing or poor-quality data. For future studies with a prospective design, this limitation should be avoided. The results of our study should not be interpreted as definitive but rather as a first step and hypothesis generator for understanding the role of the cluster of double triggering and ineffective efforts.

Although having more data is generally considered better (39), restricting the dataset ensured quality and reliability. Furthermore, data from nonelectronic medical records (reports manually written by the healthcare staff) were retrieved in 98 patients, mainly regarding the use of sedatives, analgesics, neuromuscular blockade, and monitoring thereof of depth are important variables to enhance interpretation of the impact of asynchrony on outcomes and should be addressed in future studies. Nevertheless, previous results showed that asynchronies were more prevalent in days without any drugs or in those with the combination of sedatives plus opioids, but not when considered separately (40).

The version of our software used here did not identify reverse triggering, so we cannot differentiate between double triggering originating in an inspiratory effort that persists beyond the end of the ventilator's inspiratory cycle or one originating in a mechanical insufflation that induces a diaphragmatic contraction. Similarly, reverse triggering that persists well into expiratory time could be identified and recorded as ineffective inspiratory efforts. For this reason, we grouped all detected double triggering and ineffective efforts in the same cluster, considering also that this grouping of triggering asynchronies can be a consequence of multiple etiologies, for instance, muscle weakness from nutritional factors/hyperinflation, autopositive end-expiratory pressure–induced triggering loads, and inappropriate trigger sensitivity settings. Similarly, double triggering may be a consequence

of mismatched neural: mechanical inspiratory times, artifacts, and, as was mentioned, reverse triggering. All these may conceivably have quite different effects on outcomes.

Median duration of MV in our study (8 d) was longer than in epidemiologic studies (41, 42), probably because we included only patients on MV for greater than or equal to 24 hours, thus excluding very sick patients who died during the first day less sick and patients needing MV for less than less than 24 hours. We cannot determine the translational physiologic meaning of clusters, such as changes in driving pressure or mechanical power, because our dataset comprises stored pressure support waveforms recorded from daily clinical practice without specific maneuvers (e.g., inspiratory or expiratory pauses) required to calculate driving pressure (43) or mechanical power. Additionally, during clusters of double triggering, the presence of stacked volume from the previous breath overestimates driving pressure.

CONCLUSIONS

Clusters of double triggering and ineffective inspiratory efforts occur in all patients but are under detected by clinical tools. Their power, not their number, mainly during the first 48 hours of MV is associated with increased ICU mortality, whereas their power and duration are associated with increased duration of MV and ICU stay.

DECLARATIONS

Drs. Magrans, Fernansonc Montanyà, and Blanch contributed to study concept and design. Drs. Magrans, Ferreira, Gomreirau de Haro contributed to data acquisition. Drs. Magrans, Ferreira, Blanch, Aquino-Esperanza contributed to data processing and interpretation. Drs. Magrans, Ferreira, and Sarlabous contributed to statistical analysis. Drs. Magrans, Ferreira, Sarlabous, and Aquino- Esperanza contributed to figure preparation. Drs. Magrans, Blanch, and Aquino-Esperanza contributed to drafting of the article. Drs. Magrans, Ferreira, Sarlabous, López-Aguilar, Fernandez-Gonzalo, Navarra-Ventura, Fernández, Montanyà, Kacmarek, Rué, Forné, Blanch, de Haro, and Aquino-Esperanza contributed to revision of article for important intellectual content. Drs. Magrans, Blanch, and Aquino-Esperanza

contributed to study supervision. Blanch and Aquino-Esperanza contributed to data access and responsibility, had full access to all of the data in the study, and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed the article.

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Dr. Magrans disclosed that he works for Better Care S.L., a spinoff of the Corporació Sanitaria Parc Tauli. Dr. Ferreira received funding from Better Care S.L.; she disclosed work for hire. Drs. Montanyà and Blanch disclosed that they own stock in Better Care S.L. Dr. Blanch disclosed that he is the inventor of a U.S. patent owned by the Corporació Sanitària Parc Taulí (U.S. Patent No. 12/538,940). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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The datasets generated and analyzed in the current study are available from the corresponding author on reasonable request.

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TABLE 1. Patient's Characteristics

Characteristic	Value
Patients	*N* = 180
Age (yr), median (interquartile range)	65 (54.7–74)
Sex (male), *n* (%)	120 (66)
Reason for MV, *n* (%)	
Acute respiratory failure	56 (31.1)
Pneumonia	28 (15.5)
Acute respiratory distress syndrome	4 (2.2)
Chronic obstructive pulmonary disease	5 (2.7)
Congestive heart failure	7 (3.8)
Other	12 (6.6)
Sepsis	35 (19.4)
Postsurgical	13 (7.2)
Neurologic	14 (7.7)
Multiple trauma	27 (15)
Cardiac arrest	10 (5.5)
Others	25 (13.8)
Acute Physiology and Chronic Health Evaluation II, median (interquartile range)	17 (11.7–22)
Sequential Organ Failure Assessment at admission, median (interquartile range)	7 (5–9)
Length of MV (d), median (interquartile range)	8 (4–14.2)
ICU stay (d), median (interquartile range)	12 (7.7–19)
ICU mortality, *n* (%)	44 (24.4)

MV = mechanical ventilation

TABLE 2. Estimated Coefficients[a] for the Two Competing Risks Events (Being Dead or Alive at Discharge)

Competing Risk Events	Whole Period of MV		First Period of MV		Second Period of MV	
	Coefficient, Mean (95% CI)	p	**Coefficient, Mean (95% CI)**	p	**Coefficient, Mean (95% CI)**	p
Multivariate[b]						
Death						
Total clusters/d	–1.233 (–1.77 to –0.69)	< 0.001	–0.696 (–1.11 to –0.28)	< 0.01	–1.362 (–1.93 to –0.79)	< 0.001
Mean power	0.256 (0.02–0.49)	0.03	0.349 (0.19–0.51)	< 0.001	0.197 (–0.08 to 0.48)	0.17
Mean duration	0.098 (–0.33 to 0.53)	0.65	–0.103 (–0.38 to 0.17)	0.46	0.249 (–0.28 to 0.77)	0.35
Age	0.036 (0–0.07)	0.04	0.037 (0.004–0.07)	0.03	0.038 (0–0.075)	0.04
APACHE II	0.007 (–0.05 to 0.06)	0.80	0.039 (–0.01, 0.09)	0.10	–0.026 (–0.08 to 0.03)	0.36
P×D	–0.015 (–0.03 to –0.001)	0.03	–0.017 (–0.03 to –0.01)	< 0.001	–0.013 (–0.03 to 0.005)	0.16
Alive						
Total clusters/d	0.389 (0.14–0.63)	< 0.01	0.463 (0.29–0.63)	< 0.001	0.146 (–0.10 to 0.40)	0.25
Mean power	–0.166 (–0.37 to 0.04)	0.11	–0.165 (–0.28 to –0.05)	< 0.01	0.076 (–0.21 to 0.36)	0.60
Mean duration	–0.117 (–0.42 to 0.18)	0.45	–0.032 (–0.20 to 0.14)	0.71	0.147 (–0.19 to 0.49)	0.40
Age	–0.003 (–0.01 to 0.01)	0.55	–0.004 (–0.02 to 0.01)	0.47	–0.004 (–0.02 to 0.01)	0.44
APACHE II	–0.015 (–0.05 to 0.02)	0.34	–0.03 (–0.06 to 0.002)	0.06	–0.012 (–0.05 to 0.02)	0.43
P×D	0.007 (–0.01 to 0.03)	0.51	0.009 (0.005–0.014)	< 0.001	–0.038 (–0.08 to 0)	0.06

APACHE = Acute Physiology and Chronic Health Evaluation, MV = mechanical ventilation.

[a] Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the event. Note also that clusters-related variables were squared root transformed.

[b] Multivariate approach with the total number of clusters, the mean power and the mean duration as covariates, and age and APACHE II as potential confounding variables. The interaction term of the main effects mean power and mean duration, P×D, is considered.

TABLE 3. Estimated Coefficients[a] for the Length of Mechanical Ventilation and ICU Stay According to the Negative Binomial Regression Models

Model Components	Whole Period of MV		First Period of MV		Second Period of MV	
	Coefficient, Mean (95% CI)	p	Coefficient, Mean (95% CI)	p	Coefficient, Mean (95% CI)	p
Multivariate[b]						
Length of MV						
Total clusters/d	0.115 (–0.04 to 0.27)	0.15	–0.212 (–0.33 to –0.09)	< 0.001	0.189 (0.05–0.33)	< 0.01
Mean power	0.160 (0.07 to 0.25)	< 0.001	0.019 (–0.04 to 0.08)	0.56	0.182 (0.09–0.27)	< 0.001
Mean duration	0.107 (–0.04 to 0.25)	0.14	0.091 (–0.005 to 0.19)	0.06	0.091 (–0.04 to 0.22)	0.16
Age	–0.007 (–0.01 to 0)	0.06	–0.006 (–0.02 to 0.001)	0.06	–0.006 (–0.01 to 0.001)	0.06
APACHE II	0.001 (–0.01 to 0.02)	0.89	0.005 (–0.01 to 0.02)	0.60	0.013 (–0.002 to 0.03)	0.09
P×D	–0.014 (–0.02 to –0.006)	< 0.001	–0.003 (–0.01 to 0.001)	0.12	–0.016 (–0.02 to –0.01)	< 0.001
ICU stay						
Total clusters/d	0.118 (–0.03 to 0.26)	0.11	–0.179 (–0.29 to –0.07)	< 0.01	0.185 (0.06 to 0.31)	< 0.01
Mean power	0.088 (0.006–0.17)	0.03	–0.019 (–0.08 to 0.04)	0.50	0.104 (0.02–0.19)	0.02
Mean duration	0.150 (0.02–0.28)	0.03	0.104 (0.02–0.19)	0.02	0.128 (0.008–0.25)	0.04
Age	–0.005 (–0.01 to 0.002)	0.15	–0.006 (–0.01 to 0.001)	0.09	–0.004 (–0.01 to 0.002)	0.17
APACHE II	–0.003 (–0.02 to 0.01)	0.73	0.001 (–0.01 to 0.02)	0.85	0.009 (–0.005 to 0.02)	0.21
P×D	–0.011 (–0.02 to –0.003)	< 0.01	–0.001 (–0.004 to 0.01)	0.60	–0.012 (–0.02 to –0.004)	< 0.01

APACHE = Acute Physiology and Chronic Health Evaluation, MV = mechanical ventilation.

[a]Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the response. Note also that clusters' variables were squared root transformed.

[b]Multivariate approach with the total number of clusters, the mean power and the mean duration as covariates, and Age and APACHE II as potential confounding variables. The interaction term of the main effects Mean power and mean duration, P×D, is considered.

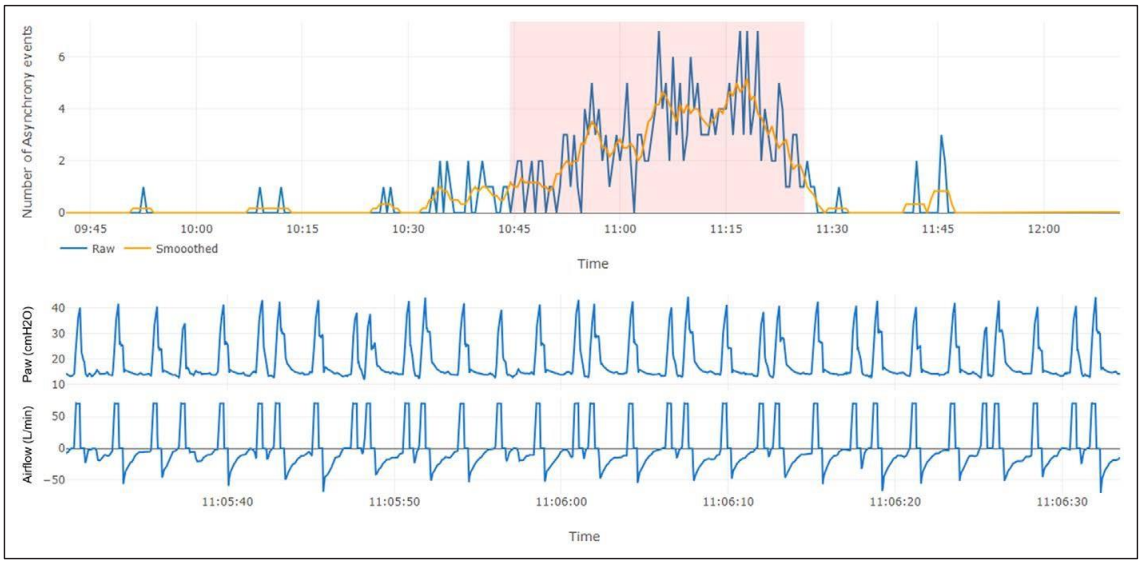

Figure 1. Representative view of a cluster of double triggering. The blue line represents the unfiltered signal of processed number of double triggering events per 30-s period. The orange line shows the smoothed signal of double triggering. The cluster is highlighted in the red shaded area and (duration measured in minutes) and power number of events in the X-axis. Starting and ending points were set at 80% of the maximum value of the smoothed time series. The pressure-time and airflow-time tracing below represent a zoomed-in segment of 1-min period within the cluster showing the detected asynchronies. Paw = airway pressure, Raw = airway resistance.

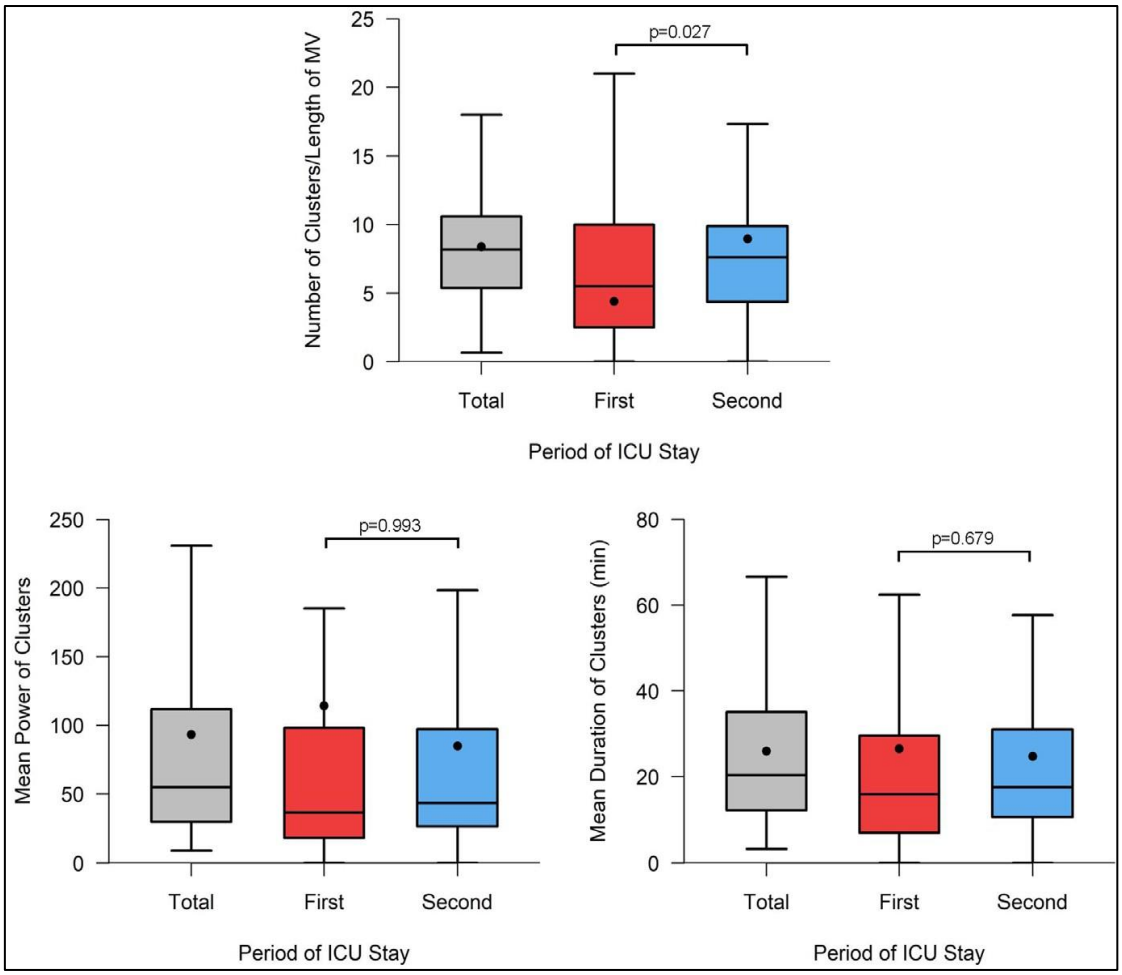

Figure 2. Boxplots of cluster characteristics in each of the three periods of mechanical ventilation (MV) analyzed. Black dots represent means, lines within boxes represent medians, and boxes include the 25th through 75th percentiles. Note that outliers have been omitted to facilitate visualization.

Online Data Supplement

The effect of clusters of double triggering and ineffective efforts in critically ill patients

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Material and Methods

Patients and data

Patients were continuously monitored at bedside with the BC Link platform (Better Care SL, Spain) (1)(2)(3), which uses drivers specifically designed to interact with the output of different medical devices rather than directly with patients. The system uses dedicated algorithms to resample, synchronize, and process airway pressure and airflow waveforms to obtain a set of physiological variables and time events; it examines each breath to determine whether one or more asynchrony events are present and stores this information in a PostgreSQL database (Berkeley, CA; https://www.postgresql.org/) for further analyses.

Asynchronies definitions and measurements

Double triggering

Double triggering (DT) or breath stacking, consists of a sustained inspiratory effort that persists beyond the ventilator's inspiratory time, triggering a second ventilator breath, which may or may not be followed by a short expiration, where all or part of the volume of the first breath is added to the second breath (4)(5). The resulting larger-than-expected tidal volume could cause ventilator-induced lung injury (6). Detection of DT was based on previously used mathematical calculations (5)(7). The system Better Care™ identifies DT when 1) expiratory time is ≥ 50% shorter than the averaged inspiratory time or 2) when two consecutive inspiratory cycles (positive flow –zero flow–positive flow) are detected with no expiration (negative flow) before the second inspiratory time. Additional information on factors influencing DT and its physiological implications are given in de Haro et al. (2).

Ineffective inspiratory efforts

Ineffective inspiratory efforts (IE) are contractions of the inspiratory muscles, primarily the diaphragm, not followed by a ventilator breath. This asynchrony occurs when the patient’s

attempt to initiate a breath does not reach the ventilator's trigger threshold; physiologically, it is characterized by an increase in transdiaphragmatic pressure (decrease in esophageal pressure, increase in gastric pressure) and/or electrical activity of the diaphragm (1)(8). Ineffective inspiratory efforts result in the patient's respiratory rate being higher than the ventilator's rate; ineffective efforts usually occur during expiration, but can also occur during the inspiratory phase.

To detect IE, Better Care™ computes a theoretical mono-exponential expiratory flow curve and compares it with the actual ones by evaluating its percentage deviation (0%=no deviation; 100%=maximum deviation). The theoretical curve results from the averaging of the 20 previous normal expirations in which there are no deviations that could represent an IEE. See Blanch et al. and Aquino-Esperanza et al., for additional information (1)(8).

Detection of clusters of asynchronies

The cluster-detection algorithm was based on Vaporidi et al.'s (9) mathematical description of clusters of ineffective inspiratory efforts. We defined a cluster as a period in which >10% of the total number of respiratory cycles contained DT and/or IE (i.e., > 6 asynchrony events in a 3-minute period assuming a respiratory rate of 20 breaths per minute). Briefly, from detected double triggering and ineffective inspiratory efforts, discrete time series were obtained for non-overlapping 30-second intervals and smoothed time series (running mean with n=6 points) were computed to identify clusters. Starting and ending points were set at 80% of the maximum value of the smoothed time series (Figure 1 of the manuscript). Because the incidence of different types of asynchronies can be lower (2) or higher than the incidence of ineffective inspiratory efforts and some asynchronies may be more harmful than ineffective inspiratory efforts, we used a lower threshold to define a cluster.

Statistical analysis

To model patients' status at ICU discharge, we used the Fine-Gray competing-risk model (10)(11)(12), which estimates the proportional subdistribution hazards of a particular type of event (discharge dead or alive from the ICU) in a setting where the occurrence of one event completely precludes the occurrence of the other. We first estimated the cumulative incidence function (CIF) for each event, and we then investigated the effects of the cluster-related variables on the CIF. Only patients who stayed >30 days in the ICU were right censored.

We used generalized linear models to investigate possible associations between the characteristics of clusters of asynchronies and ICU LoS and duration of MV; these outcome variables were assumed to follow a negative binomial distribution because they are cont variables and present overdispersion (13).

To control potential bias resulting from varying length of MV among patients, the total number of clusters was corrected for the number of days on MV in each period, (i.e., total number/days on MV). To mitigate the negative impact of some outliers in the coefficient estimations and to improve model adjustment, the square-root transformation was applied to the normalized total number of clusters, to the mean power, and to the mean duration. All models were adjusted for patient age and APACHE II as potential confounding variables. Moreover, we considered the combined effect of power and duration by including their interaction. To verify model assumptions, we used various diagnostic methods. To check the proportionality assumption of the competing risks models, we plotted the Schoenfeld residuals against the failure time for each covariate. To assess the normality of the residuals in the generalized linear models, we used Q-Q plots, and to assess the overdispersion, we plotted the standardized residuals versus the fitted values.

We used R 3.3.1 (R Core Team, Vienna, Austria; URL: http://www.R-project.org/) for all analyses. Competing risk analyses were performed with the *cmprsk* package (14). Values of $p < 0.05$ were considered significant.

Results

Predicted cumulative incidence functions for patients grouped according the status at ICU discharge (dead or alive)

For descriptive purpose, Figure E4 shows the CIF for the two studied events without considering the effects of any covariates. According to the CIF, the probabilities of being alive at discharge and of being dead at discharge were nearly identical during the first 5 days after admission (6% for dead vs. 7% for alive); however, the estimates were progressively different during the period comprising days 6 through 30 after admission (21% for dead vs. 67% for alive).

The analysis of the predicted probability of the CIF for the event being discharged alive in those patients who were actually discharged alive and the predicted probability of death in those who actually died showed that the model predicted both events accurately (i.e., assigned a high probability of being discharged alive for those who survived and a high probability of being discharged dead for those who actually died) (Figures E5 and E6).

Clinical case simulation

In order to translate our findings into a clinical setting, we simulate an example based on the profile of patients who died and patients who were discharge alive form the ICU. Our results showed that the effect of clusters characteristics (power and duration), after adjusting the model for age and APACHE II severity score, determines different probabilities for the two studied competing risk events: discharge dead or discharge alive from the ICU. Hence, in order to exemplify this, we propose two different hypothetical patients.

Patient 1: A 62 years old male with APACHE II of 17, who developed 9 clusters per day with a mean power of 42 events in each cluster and a mean duration of 16 minutes each.

Patient 2: A 72 years old male with APACHE II of 19, who developed 6 clusters per day with a mean power of 93 events in each cluster and a mean duration of 32 minutes each.

Considering that our median hospital stay was 8 days, we could now analyze how were the probabilities for the two studied outcomes for each patient.

At day 8, the probabilities of being discharge dead from the ICU for *patient 1* were: 3.2 %, and for *patient 2* were 15.2%. On the other hand, the probabilities of being discharge alive for patient 1 were 25.2% and for patient 2 were 12.3%.

Despite that *patient 1* had more clusters per day, those developed by *patient 2* were longer and with higher power. Even though they were lesser they conferred a higher probability of being discharge dead and fewer probabilities of being discharge alive. For a more illustrative example Figure E6 represents each of the probabilities for the two competing risk events.

Neuromuscular blocking agents

Due to the difficulty of accessing older medical records in paper format, information on NMB use could only be obtained for 98 patients. Of those, 11 (11.2%) received NM blockade at some point during the first 48hs, and only 2 of them during the first and second day of mechanical ventilation. For the remaining time, the use of NM blockade was: 8 (9.6%) of 83 patients on day 3, 6 (7.9%) of 76 on day 4, 2 (2.7%) of 74 on day 5, 3 (4.8%) of 62 on day 6, 2 (3.4%) of 59 on day 7, and 1 of 52 (1.9%), 49 (2%) and 40 (2.5%) on day 8, 9 and 10 respectively. Given the lack of data on NMB use for more than half of the sample and the non-repeated measures design of the model, this variable was not included as a covariate in the statistical analysis. Only clinical inferences could be made on the basis of these new findings.

Even though these data are incomplete, if they were to be considered representative of the studied population, the use of NM blockade at some point of the first 48hs in a heterogeneous critically ill patients ventilated for several reasons, might not affect the obtained results given the low rate us usage and that only 2 patients used during both days

Interpretation of the effect of the interaction term on status at ICU discharge.

To analyze whether increased power/duration of the cluster increased or decreased the probability of being discharged dead or alive from the ICU, we considered particular cases (Table E1). First, we took the mean values of all the input variables in the model (square root of total number of clusters, square root of power, square root of duration, age, and APACHE II) to simulate a patient who would be representative of the mean sample (i.e., the reference case). Second, we increased the square root of the mean power by one unit while maintaining the other variables constant and examined the estimated probabilities for each day. Third, we increased the square root of mean duration by one unit while maintaining the remaining variables constant and examined the effect on the estimated probabilities.

Table E1. Example cases used to explain the meaning of the interaction "mean power X mean duration" on patient status at ICU discharge (dead or alive).

	Total	Mean Power	Mean Duration	Age	APACHE II
Reference	2.89	9.65	5.09	62.5	16.7
Power+1	2.89	10.65	5.09	62.5	16.7
Duration+1	2.89	9.65	6.09	62.5	16.7

For interpretation, we have to emphasize two important results. As shown in Table 2 of the manuscript, the coefficients of the variables Power and Duration were positively associated with the estimated probability of dying in the ICU and negatively associated with the estimated probability of being discharged alive from the ICU; the Power x Duration interaction (P×D) is statistically significant only for being dead at discharge from the ICU (with a negative sign). Then, from Figure E2 (A), adding one unit to the square root of the mean power produced an

estimated probability curve that lies above the mean curve. On the other hand, adding one unit to the square root of the mean duration while keeping the values of all the other variables constant produced an estimated probability curve that lies below the mean curve, although the coefficient of this variable is also positive in the original model. These results are due to the statistically significant interaction between these two variables. Conversely, in Figure E2 (B), the two curves (green dashed and purple dash-dotted) lie below the mean curve, meaning the P×D interaction for the event "being discharged alive" was not statistically significant.

Concerning the analysis by periods of ICU stay (i.e., first 48 hours and the time thereafter), a similar procedure to that described in Table E1 was followed. Results are shown in Figures E2. For the first period (Figure E2 A-B), the two curves (green dashed and purple dash-dotted) clearly lie on opposite sides of the mean reference curve (black solid), which proves the statistically significant association of the interaction term with status at ICU discharge. For the second period (Figure E2 C-D), the interaction term was not significant for being discharged dead or for being discharged alive. This situation is represented by the position of the curves (green dashed and purple dash-dotted), both of which lie above or under the mean curve.

Summarizing, the higher the power of clusters, the greater the probability of being dead at discharge from the ICU. Likewise, the longer the duration of clusters, the greater the probability of being dead at discharge from the ICU if the power of the clusters also increases when the duration increases. For the mean duration of the clusters to increase the probability of being dead at discharge, it must be accompanied by more asynchronous events (i.e., greater mean power of clusters).

In other words, longer clusters with fewer asynchronous events are less "harmful" than shorter clusters with more asynchronous events. It is worth noting that the correlation between the cluster's power and duration was 0.89, which means that short clusters with very high power are highly unlikely, as well as long lasting clusters with low power.

Interpretation of the effect of the interaction term on the duration of mechanical ventilation and on the ICU length of stay.

To investigate the effect of the interaction term on the duration of mechanical ventilation (MV) and on the ICU length of stay (LoS), we used analyses similar to those described above (see Table E1). For the reference case, the estimated duration of MV was 13.4 days and the estimated ICU LoS was 17.8 days. When the square root of the mean power increased by one unit while other variables remain unchanged, the duration of MV increased to 14.6 days and ICU LoS increased to 18.3 days. When the square root of the mean duration increased by one unit, the duration of MV decreased to 13 days and ICU LoS slightly increased to 18.5 days.

Taking into account the coefficients of the mean power and the mean duration of the clusters (Table 3 main text), these results suggest that the mean power directly impacts the duration of MV and the mean duration of the clusters only produces an effect on the duration of MV if the mean power also increases. Conversely, the mean duration of the clusters directly impacts the ICU LoS without needing a simultaneous increase in the power of the clusters.

Mean effect and confidence intervals of clusters-related variables on the MV days and on the ICU length of stay are shown in Figure E7 and Figure E8, respectively. Y-axis logarithmically scaled only for purpose of visualization; and clusters-related variables square-root transformed to minimize influence of outliers.

Supplemental table 1 and 2 shown the univariate analysis of what is reported in table 1 and 2 of the manuscript, which are the multivariate results. On the other hand, supplemental table 3 and 4 shown the multivariate analysis of the effects of ineffective efforts and double triggering, respectively.

Figure E1: Cumulative incidence function (CIF) with the estimated probabilities for the model that considers the entire stay in ICU.

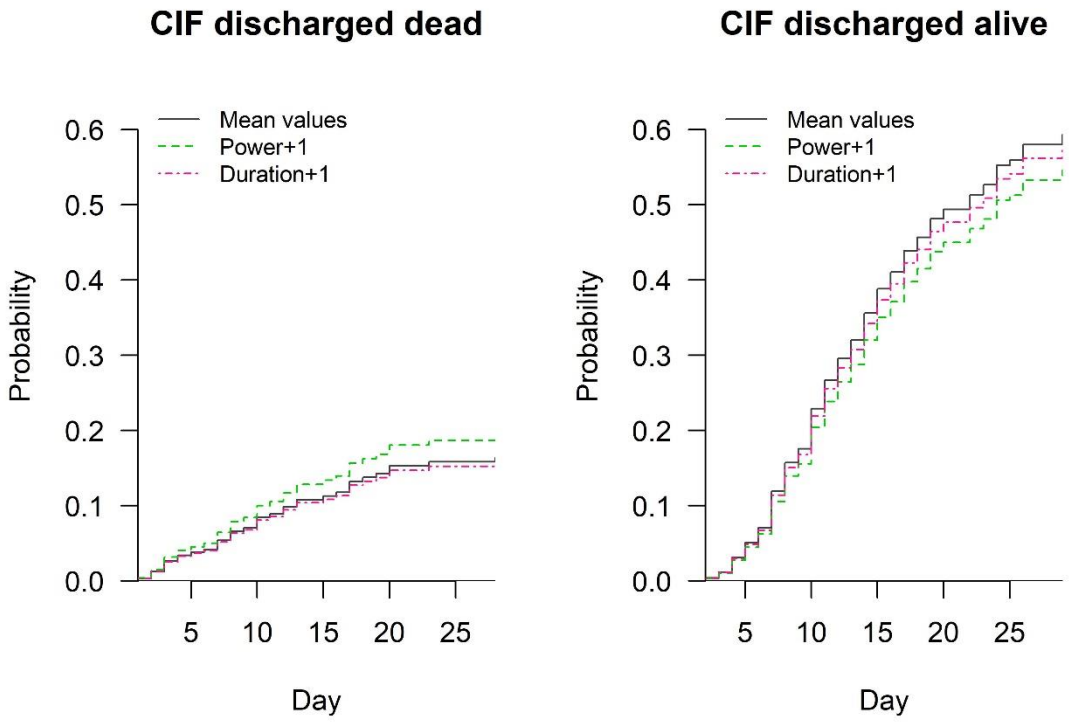

Figure E1. Mean probabilities for the events being discharged dead and being discharged alive for the reference case (black solid line); probabilities for one-unit increment of the square root of the mean power (green dashed line); probabilities for one-unit increment of the square root of the mean duration (purple dash-dotted line).

Figure E2. Estimated probabilities for the first 48 hours of mechanical ventilation and remaining time

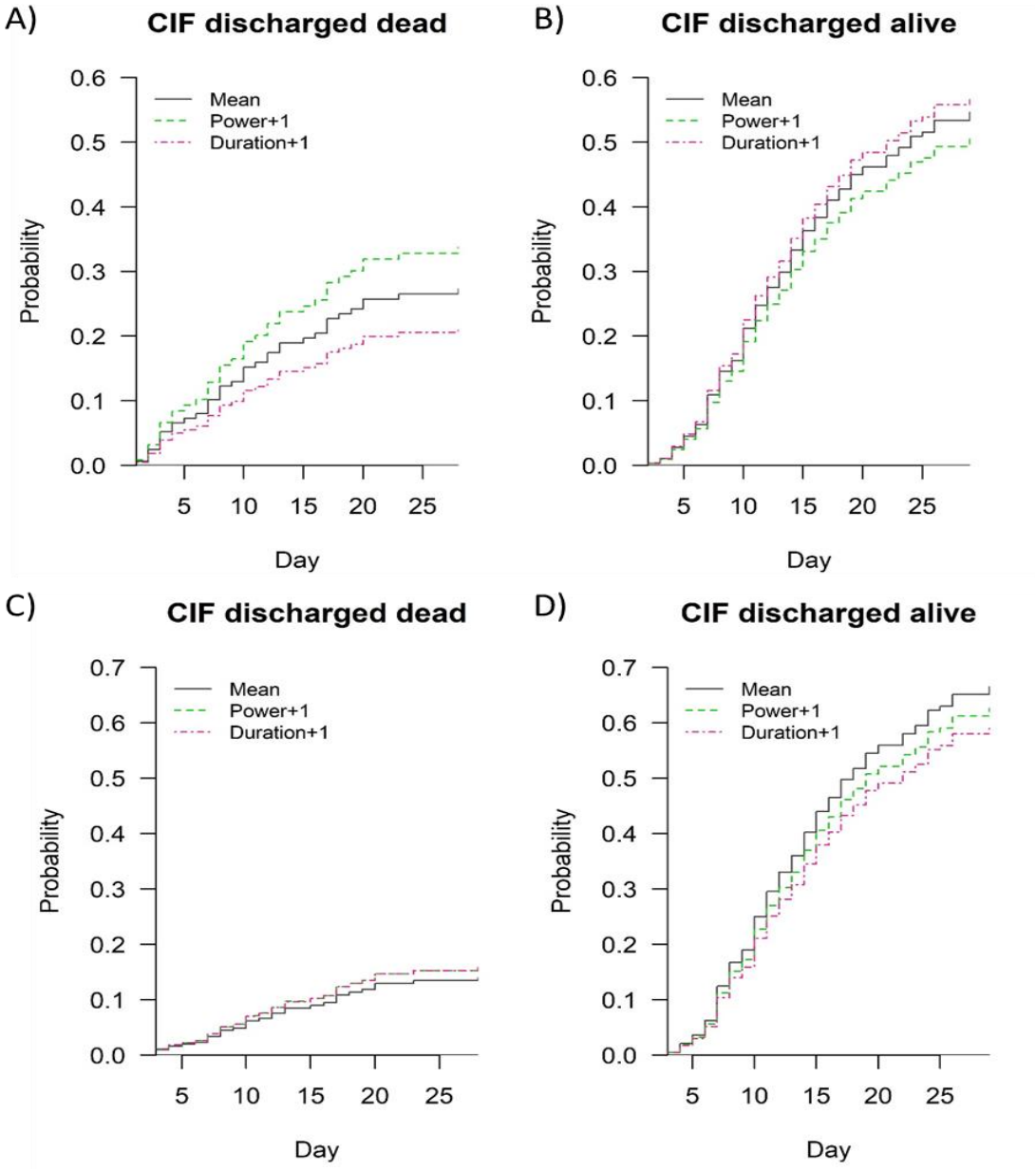

Figure E2. Mean probabilities for the events being discharged dead and being discharged alive for the reference case (black solid line); probabilities for one-unit increment of the square root of the mean power (green dashed line); probabilities for one-unit increment of the square root of the mean duration (purple dash-dotted line). Estimated probabilities for the first 48 hours (A-B) and for the second period (C-D) of mechanical ventilation.

Figure E3: Cumulative incidence function for the two studied events without considering the effects of covariates

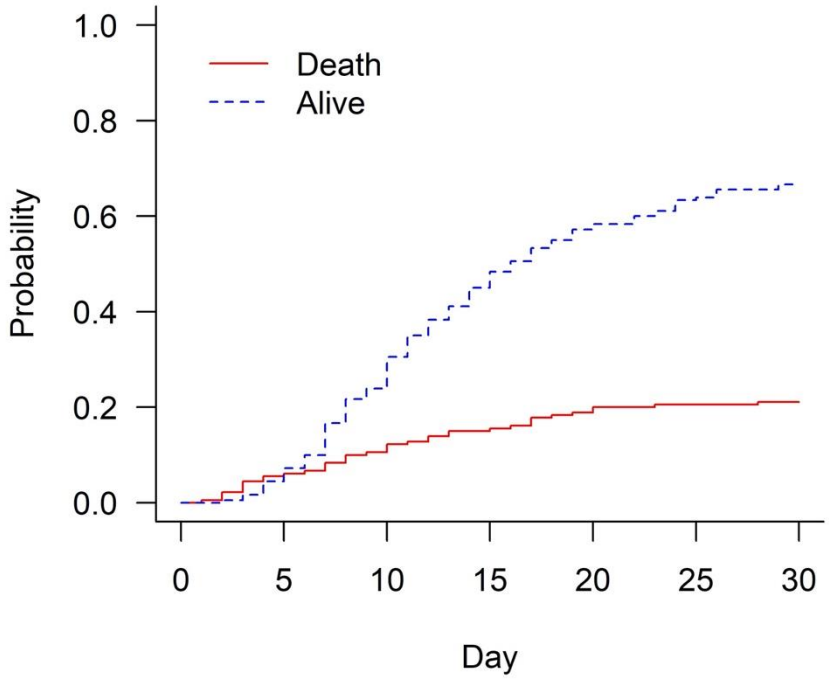

Figure E3. Cumulative incidence function showing the probability for the events being dead at ICU discharge (red line) and being alive at ICU discharge (blue line) at any following time without considering the effects of covariates. The probability is estimated as the ratio of the number of patients who experienced that event type until a specific day divided by the total number of patients, and correctly adjusted by the number of censored observations (i.e., the patients for whom the 30-day follow-up time ends before any of the two events considered were observed). Twenty-two patients were right censored at day 30.

Figure E4: Predicted cumulative incidence functions for each patient grouped according the status at ICU discharge

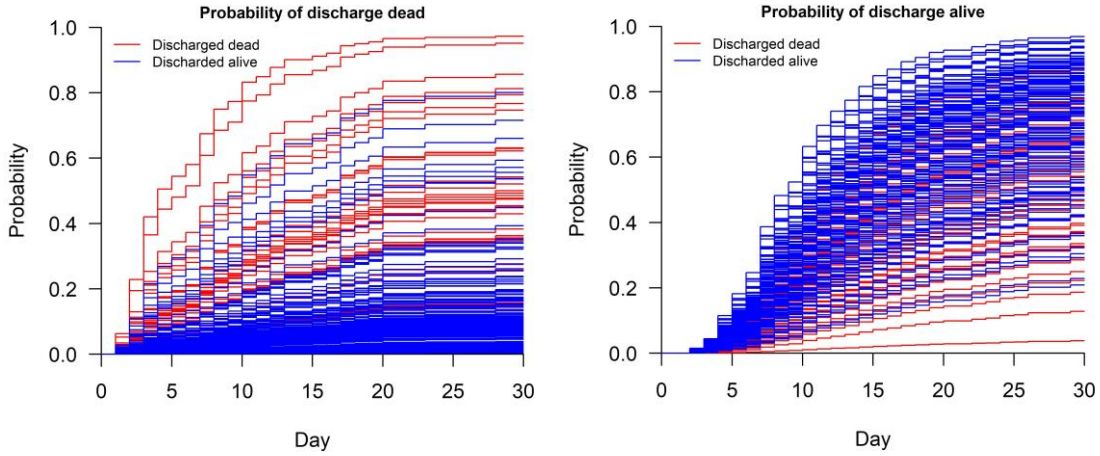

Figure E4. Predicted cumulative incidence function for the events death in the ICU (left) and being discharged alive from ICU (right) for the patients discharged dead (red lines) and alive (blue lines).

Figure E5: Predictive probability of discharge death or alive according to groups

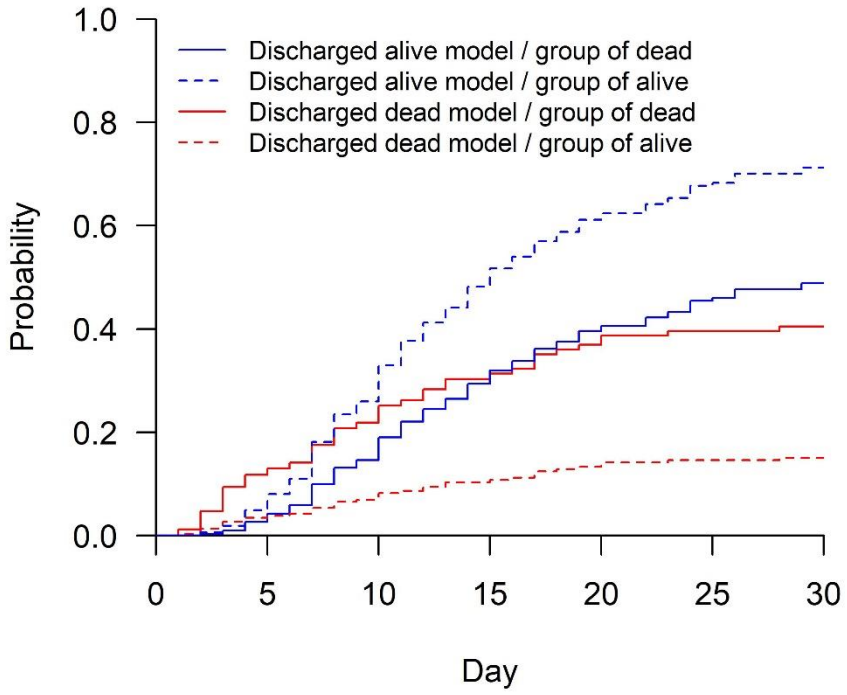

Figure E5. Predicted cumulative incidence functions for the events death in the ICU (red lines) and discharge alive from ICU (blue lines) for the mean of the group of patients discharged dead (solid lines) and discharged alive (dashed lines).

Figure E6: Distribution of the clusters-related variables according with the status at ICU discharge.

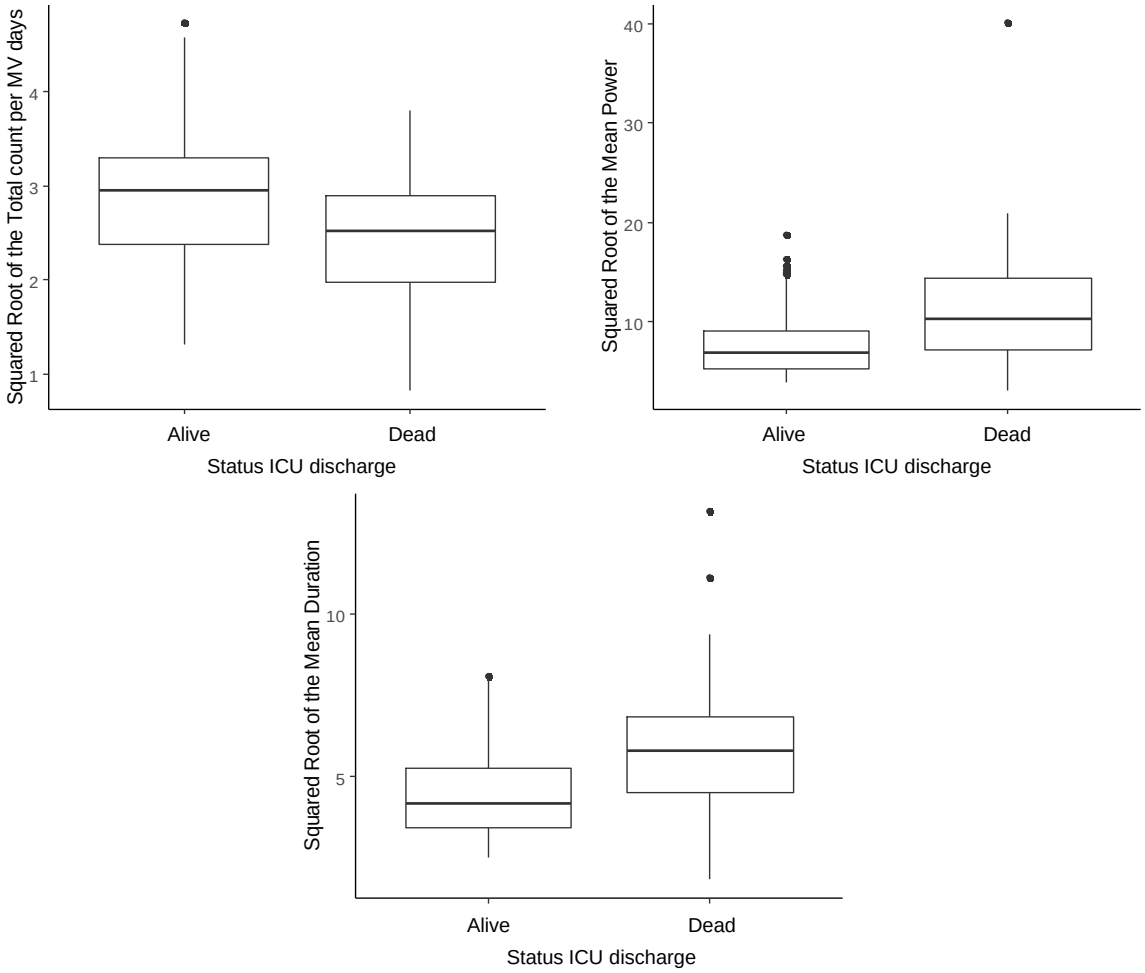

Figure E6. Exploratory boxplots showing the distribution of the clusters-related variables according with the status at ICU discharge (alive or dead). Variables were square-root transformed to minimize influence of outliers.

Figure E7: Mean effect and confidence intervals of clusters-related variables on the mechanical ventilation days.

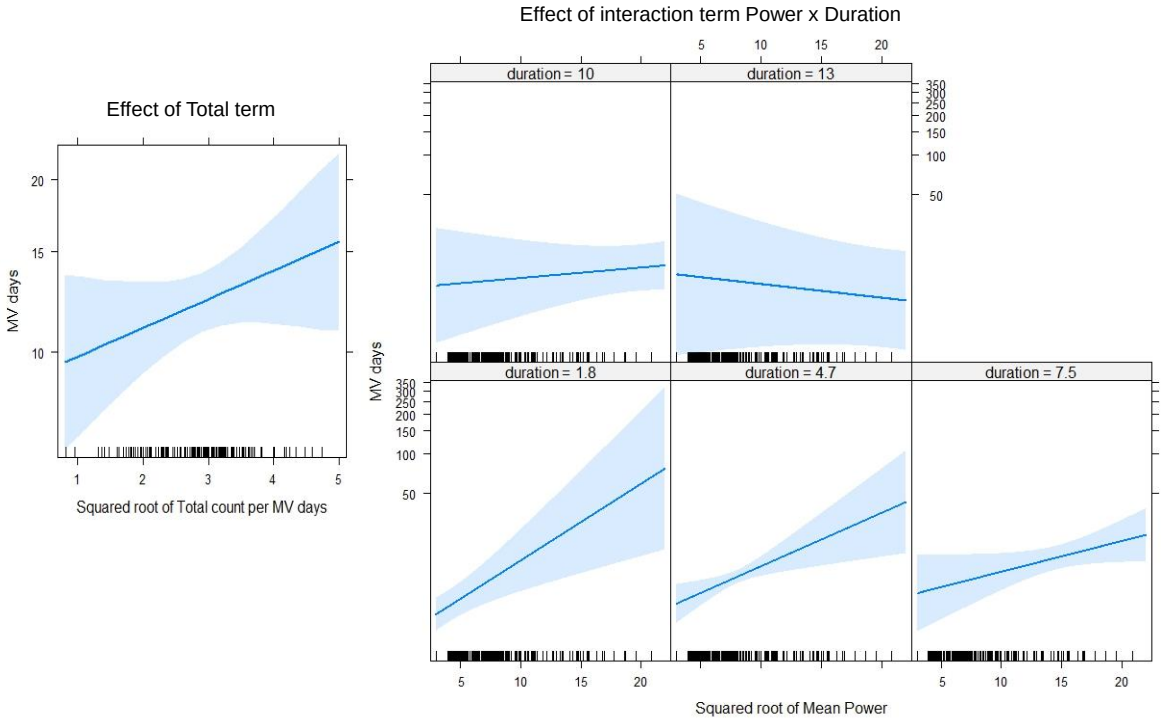

Figure E7. Effect of the total number of cluster per MV days (left plot), and of the interaction Mean Power and the Mean Duration (right plots) on the length of mechanical ventilation. Y-axis logarithmically scaled only for purpose of visualization; and clusters-related variables square-root transformed to minimize influence of outliers.

Figure 8: Mean effect and confidence intervals of clusters-related variables on the ICU length of stay.

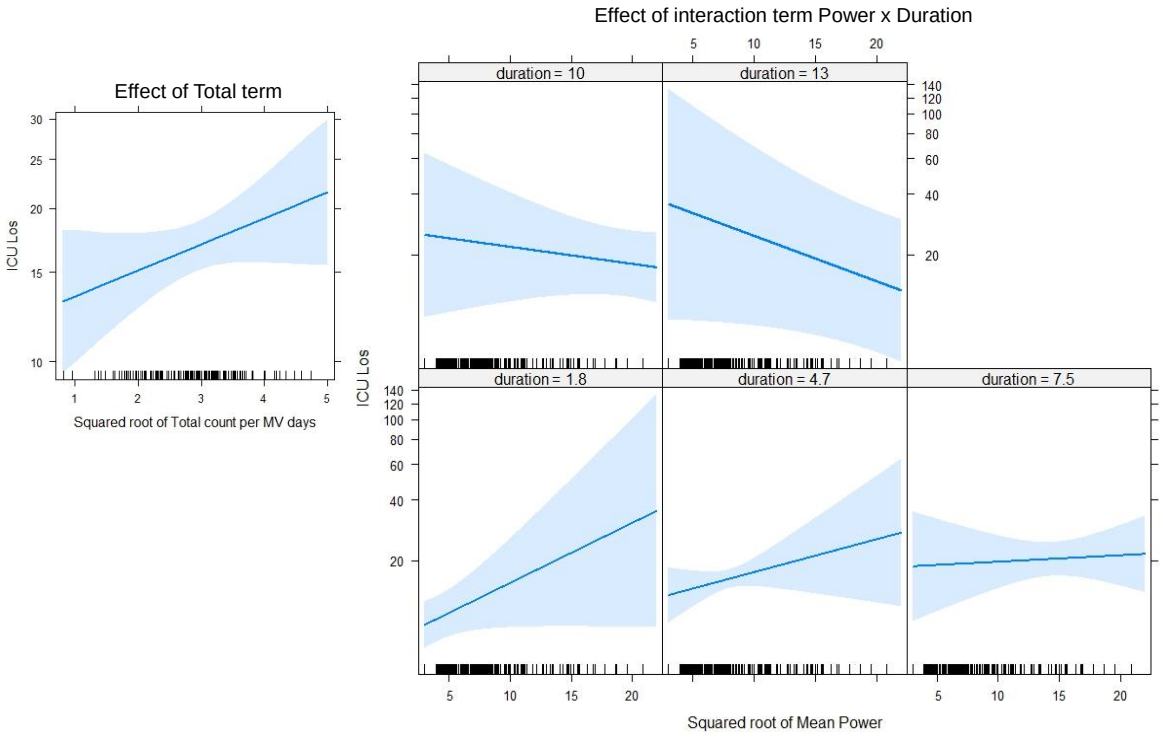

Figure E8. Effect of the total number of cluster per MV days (left plot), and of the interaction Mean Power and the Mean Duration (right plots) on the ICU length of stay. Y-axis logarithmically scaled only for purpose of visualization; and clusters-related variables square-root transformed to minimize influence of outliers.

Supplementary table 1: Estimated coefficients [a] for the two competing risks events (being dead or alive at discharge).

	Whole Period of MV		First Period of MV		Second Period of MV	
	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value
Univariate						
Death						
Total clusters/day	-0.986(-1.44, -0.53)	<0.001	-0.154(-0.39, 0.09)	0.20	-0.767(-1.15, -0.38)	<0.001
Mean power	0.099(0.06, 0.14)	<0.001	0.031(0, 0.05)	0.04	0.094(0.05, 0.14)	<0.001
Mean duration	0.323(0.18, 0.46)	<0.001	0.06(-0.03, 0.15)	0.18	0.242(-0.01, 0.50)	0.06
Age	0.038(0.01, 0.07)	<0.01				
APACHEII	0.054(0, 0.10)	0.04				
Alive						
Total clusters/day	0.306(0.06, 0.55)	0.01	0.214(0.05,0.38)	0.01	0.061(-0.16, 0.28)	0.58
Mean power	-0.129(-0.18, -0.07)	<0.001	-0.021(-0.04, 0.01)	0.13	-0.112(-0.17, -0.05)	<0.001
Mean duration	-0.275(-0.40, -0.14)	<0.001	-0.036(-0.09, 0.02)	0.19	-0.202(-0.33, -0.08)	<0.01
Age	-0.01(-0.02, 0)	0.06				
APACHEII	-0.028(-0.05, -0.001)	0.04				

[a]**:** Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the event. Note also that clusters-related variables were squared-root transformed.

CI, confidence interval. MV, mechanical ventilation

Supplementary table 2: Estimated coefficients[a] for the length of MV and ICU stay according to the negative binomial regression models.

	Whole Period of MV		First Period of MV		Second Period of MV	
	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value
Univariate						
Length of MV						
Total clusters/day	0.231(0.07, 0.39)	<0.01	-0.107(-0.20, -0.01)	0.03	0.397(0.27, 0.52)	<0.001
Mean power	0.053(0.03, 0.08)	<0.001	0.004(-0.01, 0.02)	0.62	0.083(0.06, 0.11)	<0.001
Mean duration	0.125(0.06, 0.19)	<0.001	0.013(-0.02, 0.05)	0.48	0.198(0.14, 0.26)	<0.001
Age	-0.006(-0.01, 0.002)	0.14				
APACHEII	-0.005(-0.02, 0.01)	0.54				
ICU stay						
Total clusters/day	0.198(0.05, 0.34)	<0.01	-0.117(-0.23, -0.03)	<0.01	0.339(0.23, 0.45)	<0.001
Mean power	0.028(0.005, 0.05)	0.02	-0.002(-0.02, 0.01)	0.78	0.056(0.03, 0.08)	<0.001
Mean duration	0.083(0.02, 0.14)	<0.01	0.002(-0.03, 0.04)	0.91	0.15(0.09, 0.21)	<0.001
Age	-0.004(-0.01, 0.002)	0.20				
APACHEII	-0.008(-0.02, 0.007)	0.30				

[a] Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the response. Note also that clusters' variables were squared root transformed.

CI, confidence interval. MV, mechanical ventilation

Supplementary table 3: Estimated coefficients [a] for the two competing risks events (being dead or alive at discharge) For clusters of ineffective effort only, during the whole period of MV, first 48hs and remaining time.

	Whole Period of MV		First Period of MV		Second Period of MV	
	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value	Coefficient, Mean(95%CI)	p-value
Multivariate[b]						
Death						
Total clusters/day	-0.715 (-1.34, -0.09)	0.02	-0.41 (-0.92, 0.10)	0.11	-0.71 (-1.49, 0.07)	0.08
Mean power	0.142 (-0.12, 0.40)	0.28	0.304 (0.07, 0.54)	0.01	0.16 (-0.15, 0.47)	0.32
Mean duration	-0.007 (-0.56, 0.55)	0.98	-0.369 (-0.80, 0.06)	0.09	-0.047 (-0.69, 0.60)	0.89
Age	0.035 (0, 0.07)	0.04	0.033(0, 0.06)	0.03	0.036 (0.02, 0.06)	0.04
APACHEII	0.013 (-0.05, 0.08)	0.69	0.041 (-0.02, 0.1)	0.16	-0.018 (-0.08, 0.04)	0.55
P×D	-0.004 (-0.02, 0.01)	0.58	-0.008 (-0.02, 0)	0.11	-0.003 (-0.02, 0.02)	0.69
Alive						
Total clusters/day	0.243 (-0.06, 0.55)	0.12	0.330 (0.03, 0.63)	0.03	0.104 (-0.19, 0.40)	0.49
Mean power	-0.088 (-0.33, 0.16)	0.48	-0.129 (-0.33, 0.07)	0.20	-0.111 (-0.35, 0.12)	0.38
Mean duration	0.039 (0.26, 0.34)	0.80	0.161 (-0.05, 0.38)	0.15	0.057 (-0.24, 0.35)	0.71
Age	-0.006 (-0.02, 0.01)	0.31	-0.005 (-0.01, 0)	0.33	-0.008 (-0.02, 0)	0.18
APACHEII	-0.018 (-0.02, 0.01)	0.24	-0.028 (-0.34, 0.28)	0.07	-0.019 (-0.05, 0.01)	0.23
P×D	-0.007 (-0.02, 0.02)	0.66	-0.001 (-0.02, 0.01)	0.85	-0.008 (-0.04, 0.02)	0.62

[a]**:** Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the event. Note also that clusters-related variables were squared-root transformed.

CI, confidence interval. MV, mechanical ventilation

Supplementary table 4: Estimated coefficients [a] for the two competing risks events (being dead or alive at discharge) For clusters of double triggering only, during the whole period of MV, first 48hs and remaining time.

	Whole Period of MV Coefficient, Mean(95%CI)	p-value	**First Period of MV** Coefficient, Mean(95%CI)	p-value	**Second Period of MV** Coefficient, Mean(95%CI)	p-value
Multivariate[b]						
Death						
Total clusters/day	-0.681 (-1.28, -0.08)	0.03	-0.238 (-0.70, 0.22)	0.31	-0.807 (-1.71, 0.09)	0.08
Mean power	-0.038 (-0.49, 0.41)	0.87	0.155 (-0.10, 0.33)	0.29	-0.109 (-0.67, 0.46)	0.70
Mean duration	-0.026 (-0.55, 0.50)	0.92	-0.034 (-0.32, 0.25)	0.81	-0.346 (-0.96, 0.27)	0.27
Age	0.035 (0, 0.07	0.04	0.035 (0.01, 0.06)	0.02	0.029 (0, 0.06)	0.04
APACHEII	0.031 (-0.02, 0.08)	0.25	0.032 (-0.02, 0.09)	0.25	0.011 (-0.04, 0.07)	0.69
P×D	0.025 (-0.02, 0.07)	0.28	-0.006 (-0.02, 0)	0.24	0.073 (0.01, 0.13)	0.01
Alive						
Total clusters/day	0.022 (-0.23, 0.28)	0.09	0.258 (0.02, 0.49)	0.03	0.144 (-0.10, 0.39)	0.24
Mean power	-0.009 (-0.36, 0.35)	0.96	0.041 (0.12, 0.20)	0.61	0.024 (-0.26, 0.31)	0.87
Mean duration	-0.140 (-0.53, 0.25)	0.48	-0.205 (-0.41, 0)	0.04	0.109 (-0.26, 0.47)	0.56
Age	-0.004 (-0..01, 0.01)	0.43	-0.005 (-0.01, 0)	0.31	-0.004 (-0.02, 0.01)	0.43
APACHEII	0.026 (0, 0.05)	0.07	-0.034 (-0.06, 0)	0.02	-0.017 (0.05, 0.01)	0.28
P×D	-0.006 (-0.05, 0.04)	0.75	0.001 (0, 0.01)	0.64	-0.039 (-0.08, 0)	0.06

[a]**:** Coefficients are in the logarithmic scale. The negative sign indicates an inverse association between the independent variable and the event. Note also that clusters-related variables were squared-root transformed.

CI, confidence interval. MV, mechanical ventilation

Diagnostic plots for verification of the model

To further assess the adequacy and consistency of the proposed model, diagnostic plots were used. The difference between the values obtained from the experiment and those predicted by the model is called the residual. Diagnostic plots with the Schoenfeld residuals versus the failure time for each covariate resulting from the multivariate competing risk analysis for the three periods analyzed are shown in Figure E9 (entire period), Figure E10 (first 48 hours) and Figure E11 (from 48 hours to discharge or death), respectively. In addition, the diagnostic plots of the multivariate negative binomial regression models for the duration of mechanical ventilation and the ICU length of stay for the three periods analyzed are shown in Figure E12 and Figure E13, respectively.

Figure E9:

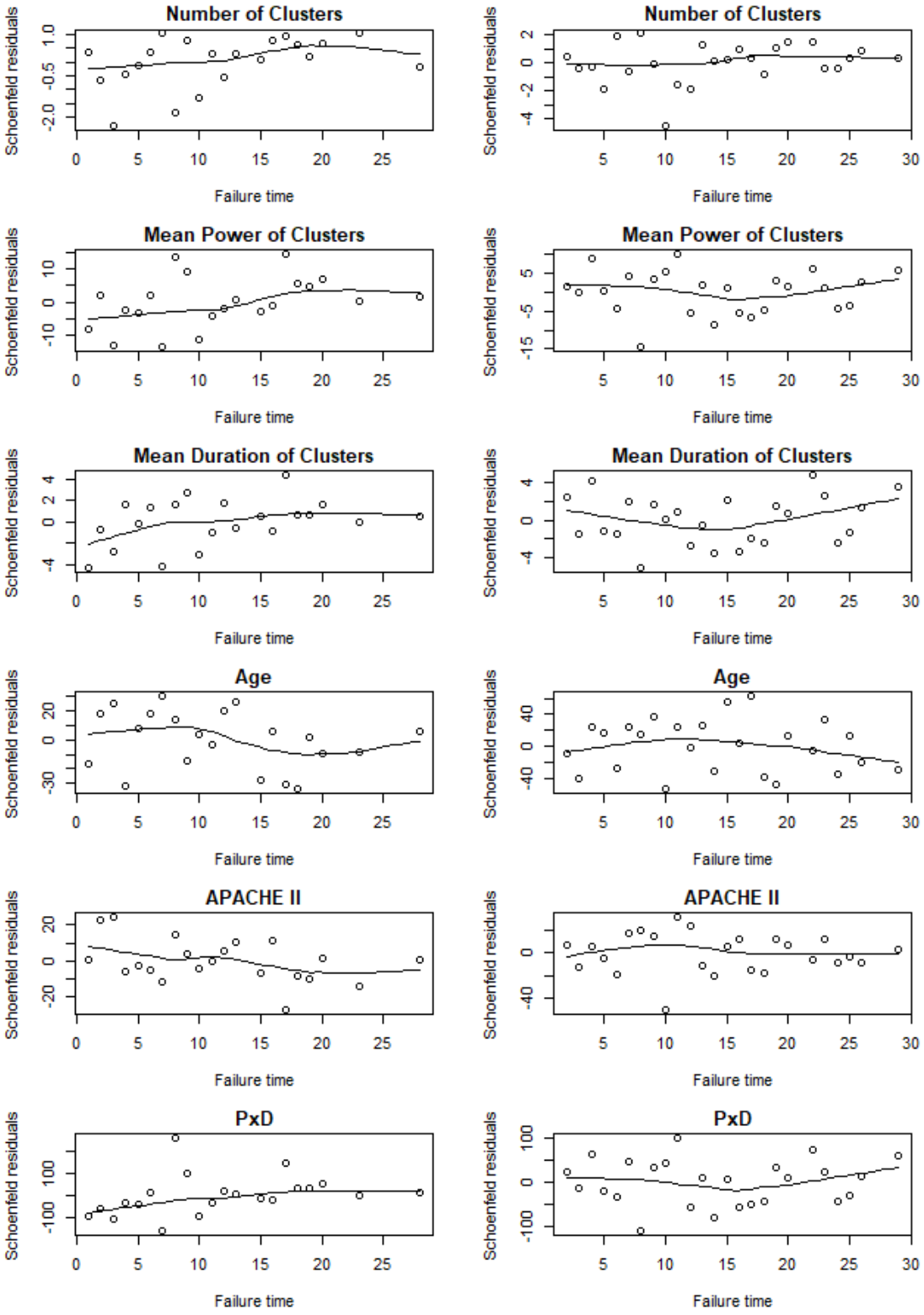
Number of Clusters
Schoenfeld residuals
Failure time
Number of Clusters
Schoenfeld residuals
Failure time
Mean Power of Clusters
Schoenfeld residuals
Failure time
Mean Power of Clusters
Schoenfeld residuals
Failure time
Mean Duration of Clusters
Schoenfeld residuals
Failure time
Mean Duration of Clusters
Schoenfeld residuals
Failure time
Age
Schoenfeld residuals
Failure time
Age
Schoenfeld residuals
Failure time
APACHE II
Schoenfeld residuals
Failure time
APACHE II
Schoenfeld residuals
Failure time
PxD
Schoenfeld residuals
Failure time
PxD
Schoenfeld residuals
Failure time

Figure E9. Diagnostic plots with the Schoenfeld residuals versus the failure time for each covariate resulting from the multivariate competing risk analysis (left panels: death, right panels: alive) for the entire period under mechanical ventilation.

Figure E10

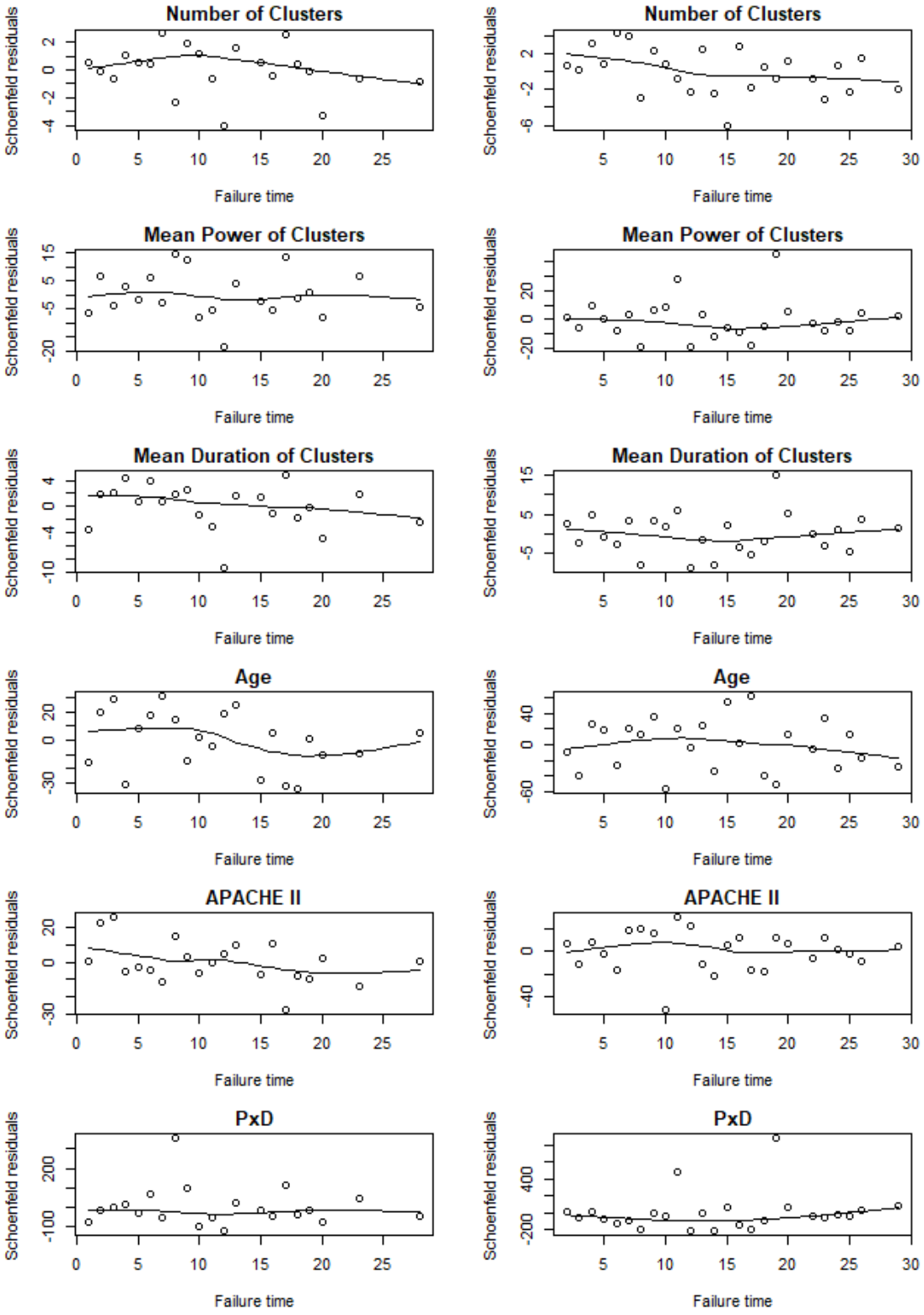
Number of Clusters
Schoenfeld residuals
Failure time
Number of Clusters
Schoenfeld residuals
Failure time
Mean Power of Clusters
Schoenfeld residuals
Failure time
Mean Power of Clusters
Schoenfeld residuals
Failure time
Mean Duration of Clusters
Schoenfeld residuals
Failure time
Mean Duration of Clusters
Schoenfeld residuals
Failure time
Age
Schoenfeld residuals
Failure time
Age
Schoenfeld residuals
Failure time
APACHE II
Schoenfeld residuals
Failure time
APACHE II
Schoenfeld residuals
Failure time
PxD
Schoenfeld residuals
Failure time
PxD
Schoenfeld residuals
Failure time

Figure E10. Diagnostic plots with the Schoenfeld residuals versus the failure time for each covariate resulting from the multivariate competing risk analysis (left panels: death, right panels: alive) for the first period of mechanical ventilation (first 48 hours).

Figure E11

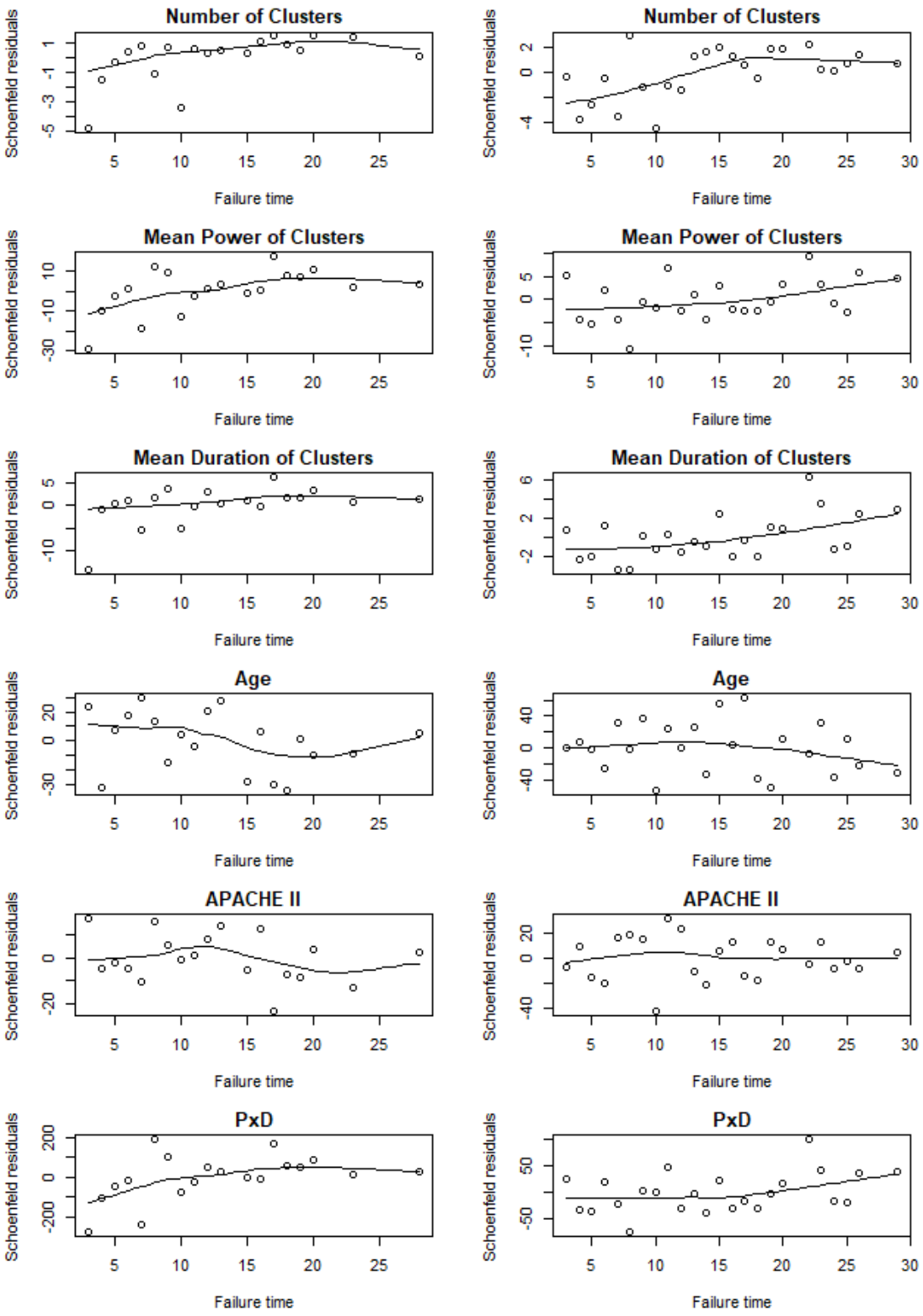

Figure E11. Diagnostic plots with the Schoenfeld residuals versus the failure time for each covariate resulting from the multivariate competing risk analysis (left panels: death, right

panels: alive) for the second period of mechanical ventilation (from 48 hours to discharge or death).

Figure E12.

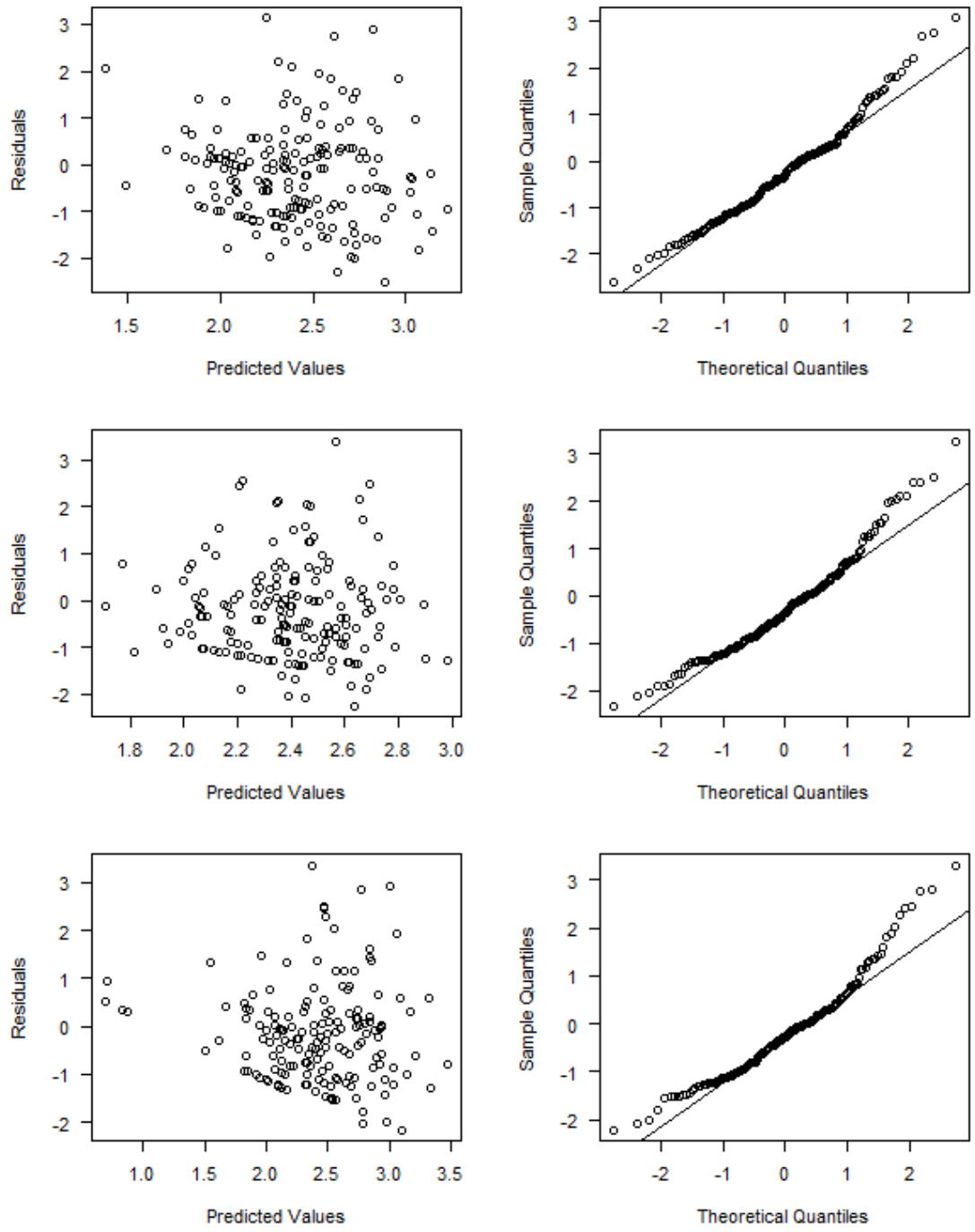

Figure E12. Diagnostic plots of the multivariate negative binomial regression models for the duration of mechanical ventilation for the three periods analyzed: entire ICU stay (top), first 48 hours (middle), and from 48 hours to discharge or death (bottom). Left, plots of residuals versus

fitted values to account for overdispersion; right, Q-Q plots to assess deviation of residuals from normality.

Figure E13.

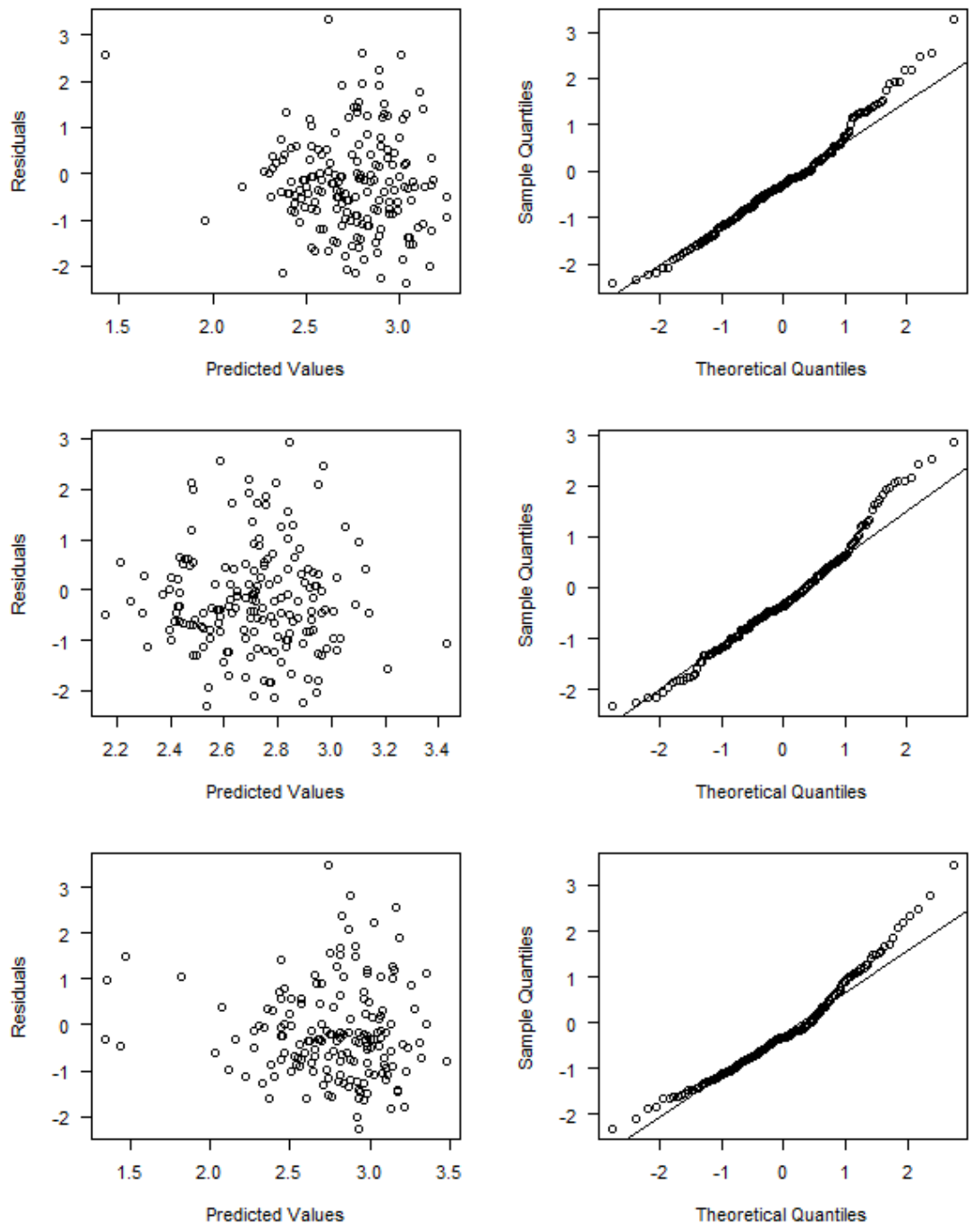

Figure E13. Diagnostic plots of the multivariate negative binomial regression models for the ICU length of stay for the three periods analyzed: entire ICU stay (top), first 48 hours (middle), and from 48 hours to discharge or death (bottom). Left, plots of residuals versus fitted values to account for overdispersion; right, Q-Q plots to assess deviation of residuals from normality.

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