Prognostic factors and outcomes of unplanned extubation

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This study investigated the prognostic factors and outcomes of unplanned extubation (UE) in patients in a medical center’s 6 intensive care units (ICUs) and calculated their mortality risk. We retrospectively reviewed the medical records of all adult patients in Chi Mei Medical Center who underwent UE between 2009 and 2015. During the study period, there were 305 episodes of UE in 295 ICU patients (men: 199 [67.5%]; mean age: 65.7 years; age range: 18–94 years). The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 16.4, mean therapeutic intervention scoring system (TISS) score was 26.5, and mean Glasgow coma scale score was 10.4. One hundred thirty-six patients (46.1%) were re-intubated within 48 h. Forty-five died (mortality rate: 15.3%). Multivariate analyses showed 5 risk factors—respiratory rate, APACHE II score, uremia, liver cirrhosis, and weaning status—were independently associated with mortality. In conclusion, five risk factors including a high respiratory rate before UE, high APACHE II score, uremia, liver cirrhosis, and not in the process of being weaned—were associated with high mortality in patients who underwent UE.

Endotracheal intubation with mechanical ventilation (MV) support is an important intervention for managing patients with respiratory failure in the intensive care unit (ICU). After the respiratory condition has stabilized and the patient has been successfully weaned from MV, removal of the endotracheal tube removal (extubation) is scheduled. However, 2–16% of patients on MV undergo potentially life-threatening unplanned extubation (UE), which is defined as an accidental or a patient-induced removal of an endotracheal tube1–6. UE can cause several serious complications: aspiration pneumonia, bronchospasm, arrhythmia, respiratory failure, or even sudden cardiac arrest7–10. Furthermore, patients who undergo UE will have their MV, ICU stay, and hospital stay prolonged6, 11–13. The hospital mortality rate of patients who undergo UE can range from 10% to 25%, and even higher for patients who require reintubation6, 12, 14, 15. Although many studies6, 8, 9, 11, 12, 16–19 have mentioned UE-associated mortality, most of them focus on a comparison of mortality rates between patients who do and do not undergo UE. Some studies8, 11, 16, 19 have reported that UE is associated with a higher mortality rate, but others6, 12, 17, 18 have reported contrary findings. In the present study, we retrospectively reviewed the outcomes of patients who underwent UE in a medical center’s ICUs and calculated their mortality risk.

Methods
Study design and patient selection. A retrospective review of the medical records of all medical and surgical adult patients, including those in the 96 beds in Chi Mei’s 6 ICUs, who underwent UE between 2009 and 2015 was done in Chi Mei Medical Center. We calculated only the data of first UE for patients who underwent more than one UE during the same admission.

In our ICU, we would opiate agents including fentanyl or morphine as analgesia and benzodiazepines, including midazolam, lorazepam or propofol as sedative agents to keep patients being not agitated and comfortable according to the sedative protocol (appendix 1)15. Additionally, haloperidol can be prescribed for delirium and muscle relaxant including pancuronium or atracurium can be added if the above treatment failed. In addition, a weaning protocol was applied for the patients with acute respiratory failure ready for weaning (appendix 2). We also has set up a multidisciplinary team as physical therapist, respiratory therapist, critical care nurse and family to initiate the 4-level early mobilization program to improve the MV patients outcomes since April 1 201420. In
Died (mortality rate: 15.3%) (Table 1). One hundred ninety-nine patients (67.5%) were men only enrolled the first episode of UE for analysis, the first episodes of 295 patients were taken into further analysis. Between January 1, 2009, and December 31, 2015, there were 305 episodes of UE in 295 ICU patients. Because we only enrolled the first episode of UE for analysis, the first episodes of 295 patients were taken into further analysis. Forty-five patients died (mortality rate: 15.3%) (Table 1). One hundred ninety-nine patients (67.5%) were men (mean age = 65.7 years; age range = 18–94 years). The average APACHE II score was 16.4, TISS score was 26.5, and GCS score was 10.4. The average duration between time of intubation and UE was 134.4 ± 158.9 hours. One hundred thirty-six (46.1%) patients reintubated within 48 hours. The reasons for re-intubating patients within acute weaning and the extubation protocol, or an order by an intensivist. Extubation was considered successful to well secure oral endotracheal tube. After the clinical condition improved and hemodynamic status became regression model. SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for all analyses. Statistical analyses. The comparison between non-survivors and survivors were examined using independent-samples  $t$ test for variables which were normally distributed and Mann–Whitney U test and $\chi^2$ test for those which were not. If $P < 0.05$, it was defined statistically significant. The variable with statistical significance in univariate analysis ($P < 0.05$), were further regarded as a focused risk factor of morality in the logistic regression model. SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for all analyses. Results

Between January 1, 2009, and December 31, 2015, there were 305 episodes of UE in 295 ICU patients. Because we only enrolled the first episode of UE for analysis, the first episodes of 295 patients were taken into further analysis. Forty-five patients died (mortality rate: 15.3%) (Table 1). One hundred ninety-nine patients (67.5%) were men (mean age = 65.7 years; age range = 18–94 years). The average APACHE II score was 16.4, TISS score was 26.5, and GCS score was 10.4. The average duration between time of intubation and UE was 134.4 ± 158.9 hours. One hundred thirty-six (46.1%) patients reintubated within 48 hours. Stroke (n = 93 [31.5%]) and diabetes mellitus (n = 73 [24.8%]) were the two most common comorbidities. Non-survivors had significantly higher APACHE II score, TISS score and GCS; (3) respiratory parameter and the result of laboratory examinations before extubation, such as respiratory rate (RR), the setting of ventilatior (positive end expiratory pressure [PEEP], tidal volume [TV] and etc.); and (4) outcomes: the UE and the duration of intubation before UE, and ICU type (medical or surgical); (2) disease severity (n = 250) Non-survivors (n = 45) Survivors (n = 250) $p$ value

| Item | All patients (n = 295) | Non-survivors (n = 45) | Survivors (n = 250) | $p$ value |
|------|------------------------|------------------------|---------------------|-----------|
| Age (years) | 65.7 ± 16.1 (18–94) | 68.0 ± 14.6 | 65.4 ± 16.3 | 0.317 |
| Female patients | 96 (32.5%) | 11 (24.4%) | 85 (34.0%) | 0.208 |
| Body mass index | 23.7 ± 4.5 (13.8–41.3) | 24.0 ± 5.0 | 23.6 ± 4.4 | 0.591 |
| APACHE II score | 16.4 ± 8.7 (3–42) | 22.9 ± 8.7 | 15.2 ± 8.1 | <0.001 |
| TISS | 26.5 ± 9.1 (10–56) | 30.3 ± 10.7 | 25.9 ± 8.6 | 0.015 |
| Glasgow Coma Scales | 10.3 ± 4.1 (3–15) | 9.4 ± 4.5 | 10.5 ± 4.0 | 0.129 |
| Intubation by pulmonary cause | 112 (38.0%) | 22 (48.9%) | 90 (36.0%) | 0.101 |
| Time of MV before UE (h) | 134.4 ± 158.9 (0–1231) | 165.2 ± 239.7 | 128.8 ± 139.3 | 0.680 |
| Re-intubation within 48 h | 136 (46.1%) | 34 (75.6%) | 102 (40.8%) | <0.001 |
| Medical origin | 154 (52.2%) | 32 (71.1%) | 122 (48.8%) | 0.004 |
| Endotracheal intubation | 278 (94.2%) | 45 (100%) | 233 (93.2%) | 0.118 |
| Self-extubation | 189 (64.1%) | 27 (60.0%) | 162 (64.8%) | 0.537 |
| Co-morbidity | 1.0 ± 1.0 | 1.4 ± 1.1 | 1.0 ± 1.0 | 0.009 |
| Coronary artery disease | 71 (24.1%) | 10 (22.2%) | 61 (24.4%) | 0.753 |
| COPD | 42 (14.2%) | 6 (13.3%) | 36 (14.4%) | 0.850 |
| Liver cirrhosis | 14 (4.7%) | 9 (20.0%) | 5 (2.0%) | <0.001 |
| Diabetes | 73 (24.7%) | 16 (35.8%) | 57 (22.8%) | 0.068 |
| Stroke | 93 (31.5%) | 10 (22.8%) | 83 (33.2%) | 0.145 |
| Cancer | 24 (8.1%) | 8 (17.8%) | 16 (6.4%) | 0.017 |

Table 1. Demographic and clinical variables of the different unplanned extubation (UE) groups. Expressed as mean ± SD (range) or n (%); APACHE II = Acute Physiology and Chronic Health Evaluation; TISS = Therapeutic Intervention Score System; COPD = chronic obstructive pulmonary disease. *The Mann–Whitney U test was used owing to not being normally distributed.
good candidates for extubation; thus, their mortality risk might be higher. In contrast, the mortality was significantly associated with a higher risk of death in UE patients. This is because patients with tachypnea just before UE are not UE patients in a surgical ICU. In addition, we found that a higher respiratory rate before extubation was associated with mortality and reintubation, chronic neurological disease, emergency surgery, and higher APACHE II scores in (62.7%) as compared to those who were not (37.7%), and those successful weaning UE patients certainly had form MV over 48 hours among UE patients were higher in those MV modes were setting in weaning condition significantly lower in UE patients being weaned before extubation. Our previous study showed that the rate of liberation we has conducted an early mobilization program since April 2014 and it may help to restore the muscle power should be ready for extubation, if it occurs a little earlier than anticipated, it might not affect outcome. In addition, Non-survivors had non-significantly longer hospital stays, and higher hospital costs than did survivors. We compared the laboratory results before UE between the non-survivors and survivors (Table 2). Non-survivors had significantly higher respiratory rates, higher FiO2 requirements, higher PEEP levels, and higher agitation, and need for and use of sedatives medications were not significantly different between survivors and non-survivors. Finally, non-survivors were prescribed and took lorazepam significantly more frequently than did survivors. Survivors also had a higher percentage of weaning stats (defined as the use of pressure support mode with a pressure level ≤14 cm H2O) than did non-survivors.

Non-survivors had significantly longer hospital stays, and higher hospital costs than did survivors. Non-survivors had significantly longer ICU stays than did survivors (Table 3). Multivariate analyses showed five risk factors—respiratory rate, APACHE II score, uremia, liver cirrhosis, and weaning stats—independently associated with mortality in UE patients (Table 4).

**Discussion**

We found that a higher respiratory rate before UE, higher APACHE II score, uremia, liver cirrhosis, and not in the process of being weaned were independently associated with increased mortality in patients with UEs. This is consistent with the findings of other ICU studies. One Korean study reported the association between hospital mortality and reintubation, chronic neurological disease, emergency surgery, and higher APACHE II scores in UE patients in a surgical ICU. In addition, we found that a higher respiratory rate before extubation was associated with a higher risk of death in UE patients. This is because patients with tachypnea just before UE are not good candidates for extubation; thus, their mortality risk might be higher. In contrast, the mortality was significantly lower in UE patients being weaned before extubation. Our previous study showed that the rate of liberation form MV over 48 hours among UE patients were higher in those MV modes were setting in weaning condition (62.7%) as compared to those who were not (37.7%), and those successful weaning UE patients certainly had a significantly lower in-hospital mortality than failed UE patients (11.1% vs. 23.1%) Because these patients should be ready for extubation, if it occurs a little earlier than anticipated, it might not affect outcome. In addition, we has conducted an early mobilization program since April 1 2014, and it may help to restore the muscle power

| Item                  | All patients (n = 295) | Non-survivors (n = 45) | Survivors (n = 250) | p value |
|-----------------------|------------------------|------------------------|---------------------|---------|
| Mean arterial pressure (mmHg) | 98.0 ± 17.7 (50~153) | 93.9 ± 23.0 | 98.8 ± 16.5 | 0.185   |
| Heart rate (beats/min) | 92.4 ± 17.1 (52~152) | 95.0 ± 19.0 | 91.9 ± 16.7 | 0.365   |
| Respiratory rate (/min) | 17.6 ± 5.7 (7~36) | 19.3 ± 6.1 | 17.3 ± 5.5 | 0.026   |
| Arterial blood gas data |                        |                        |                    |         |
| pH                    | 7.43 ± 0.06 (7.13~7.59) | 7.40 ± 0.09 | 7.44 ± 0.05 | 0.015   |
| PaO2 (mmHg)           | 107.7 ± 56.1 (24~506) | 104.6 ± 65.2 | 108.3 ± 54.5 | 0.695   |
| FiO2 (%)              | 31.5 ± 12.7 (21~100) | 36.8 ± 19.1 | 30.2 ± 10.2 | 0.029   |
| PaO2/FiO2 (mmHg)      | 346.9 ± 131.9 (24~506) | 313.8 ± 170.7 | 352.9 ± 123.0 | 0.152   |
| PaCO2 (mmHg)          | 37.1 ± 8.3 (15.4~75.7) | 36.7 ± 9.5 | 37.1 ± 8.1 | 0.802   |
| Tidal volume (mL)     | 508.6 ± 152.1 (209~1458) | 501.3 ± 132.3 | 510.0 ± 155.7 | 0.542   |
| PEEP (cmH2O)          | 5.9 ± 1.6 (0~14) | 7.1 ± 2.2 | 5.6 ± 1.4 | <0.001  |
| Biochemistry data     |                        |                        |                    |         |
| Hb                    | 10.9 ± 2.0 (5.0~18.0) | 10.2 ± 2.5 | 11.1 ± 1.8 | 0.012   |
| Hct                   | 33.5 ± 7.0 (5.1~52.3) | 31.0 ± 8.7 | 33.9 ± 6.6 | 0.013   |
| BUN                   | 31.3 ± 23.3 (3~163) | 48.7 ± 35.3 | 28.1 ± 19.1 | <0.001* |
| Creatinine            | 1.9 ± 2.5 (0.4~26.2) | 2.7 ± 2.2 | 1.8 ± 2.5 | 0.024   |
| Sodium                | 139.3 ± 6.3 (112.4~161.3) | 138.6 ± 8.4 | 139.4 ± 5.9 | 0.542   |
| Potassium             | 3.9 ± 0.5 (2.6~5.9) | 3.9 ± 0.6 | 3.8 ± 0.5 | 0.713   |
| Calcium               | 7.9 ± 0.9 (1.2~12.4) | 8.0 ± 1.0 | 7.9 ± 0.9 | 0.579   |
| Phosphate             | 3.6 ± 1.8 (1.3~12.4) | 4.2 ± 2.4 | 3.5 ± 1.6 | 0.292   |
| Albumin               | 2.7 ± 0.7 (0.9~4.4) | 2.4 ± 0.7 | 2.8 ± 0.7 | 0.003   |
| UE shift              |                        |                        |                    | 0.234   |
| Day time              | 102 (34.7%) | 14 (31.3%) | 88 (35.2%) |         |
| Evening time          | 112 (38.0%) | 14 (31.1%) | 98 (39.2%) |         |
| Night time            | 81 (27.5%) | 17 (37.8%) | 64 (25.6%) |         |
| Agitation             | 95 (32.2%) | 13 (28.9%) | 82 (32.8%) | 0.605   |
| Sedatives             | 100 (33.9%) | 17 (37.8%) | 83 (33.2%) | 0.550   |
| Use of Lorazepine     | 24 (8.1%) | 9 (20.0%) | 15 (6.0%) | 0.005   |
| Weaning status        | 159 (53.9%) | 12 (26.7%) | 147 (58.8%) | <0.001  |

*The Mann-Whiney U test was used owing to not being normally distributed.

Table 2. Most recent data before extubation of different unplanned extubation (UE) groups. Expressed as mean ± SD (range) or n (%).
during the critical phase, shorten the MV days and set patients ready for weaning. Those can partially help explain UE patients under weaning trial have a better outcome.

Uremia patients usually have multiple comorbidities and are prone to develop acute organ failure and in-hospital mortality. Our previous study displayed that the uremia patients had a significantly higher incidence of mortality than non-uremia patients among patients with acute respiratory failure requiring MV (342.30 vs. 179.67 per 1000 person-years, adjusted hazard ratio of 1.43)23. In this study, we have the similar finding that uremia was associated with higher risk of death among patients with UE.

Liver cirrhosis, in adults worldwide has become the 14th most common cause of death, with an average year mortality of 1.03 million deaths23. In patients with decompensated liver cirrhosis, they would be accompanied with variceal bleeding, ascites, peritonitis, hepatorenal syndrome and hepatopulmonary syndrome. We previously showed that among critically ill patients with MV, those who with liver cirrhosis had more organ failures and had a significantly lower survival rate than non-cirrhosis controls (adjusted hazard ratio of 1.38)13. Similarly, the present study exhibited that cirrhosis could predict hospital mortality after the occurrence of UE.

More than 90% of our UE patients survived to discharge. This finding might imply that the extubation, planned and unplanned, of some patients in this study was delayed. Despite the weaning and extubation protocols of the six ICUs, the final decision to extubate could also be made by intensivists; therefore, it was possible to delay extubation. Finally, delayed extubation might have led to a relatively lower mortality rate in this study.

One recent review25 reported that reintubation rates range from 1.8% to 88% in UE patients. We found that 136 (46.1%) patients required reintubation within 48 hours after UE, and that the mortality rate of UE patients who required reintubation was higher than for patients who did not: 25.0% (34/136) vs. 6.9% (11/159). This is consistent with previous studies14,20,26. Overall, reintubation was associated with poorer outcomes in UE patients.

Other studies25,27,28 have reported several risk factors of UE: male gender, higher APACHE scores (≥17), chronic obstructive pulmonary disease, restlessness and agitation, lower sedation levels, higher consciousness levels, taking midazolam, and needing physical restraints. This is consistent with our findings on gender, the chronic obstructive pulmonary disease, restlessness and agitation, lower sedation levels, higher consciousness levels, taking midazolam, and needing physical restraints. This is consistent with our findings on gender, the mean APACHE II score, agitation, and sedation.

This study had one major limitation: it was conducted in a single medical center. There might be differences about weaning and extubation decisions between our hospital and others. Therefore, our findings might not be generalizable to other hospitals. Additional large-scale studies are warranted to confirm our findings. In addition, we find that tachypnea prior to UE is a significant finding that predicts mortality. There are many reasons for tachypnea and since the PaCO2 is not significant between groups, it is obviously not indicative of ventilation failure. Also, we did not show the tidal volume in ml/kg, as it might help to give an indicator as to their method of ventilation and determine if it is appropriate. Further survey is necessary to confirm these conclusions.

In conclusion, we found that a higher respiratory rate before UE, higher APACHE II score, uremia, liver cirrhosis, and not in the process of being weaned were risk factors associated with increased mortality in UE patients.

### Table 3. Outcomes of different unplanned extubation groups. Expressed as mean ± SD (range); NTD = new Taiwan dollars. *The Mann-Whiney U test was used owing to not being normally distributed.

| Item                  | All patients (n = 295) | Non-survivors (n = 45) | Survivors (n = 250) | p value |
|-----------------------|------------------------|------------------------|---------------------|---------|
| ICU stay (days)       | 14.7 ± 13.9 (1–127)    | 21.3 ± 21.7            | 13.5 ± 11.7         | 0.006*  |
| Hospital stay (days)  | 36.1 ± 27.1 (1–206)    | 39.7 ± 37.6            | 35.5 ± 24.8         | 0.924*  |
| Hospital cost (NTD × 10^5) | 55.8 ± 45.7 (2.1–558.5) | 67.9 ± 86.3           | 41.7 ± 35.9         | 0.004*  |

### Table 4. Mortality predictors of unplanned extubation using logistic regression model. n = 295.

| Variables             | Odds ratio | 95% confidence interval | p value |
|-----------------------|------------|-------------------------|---------|
| APACHE II             | 1.058      | 1.006                   | 1.114   | 0.028   |
| Comorbidity           | 1.247      | 0.855                   | 1.821   | 0.252   |
| Uremia                | 5.811      | 1.566                   | 21.559  | 0.009   |
| Liver cirrhosis       | 5.920      | 1.463                   | 23.96   | 0.013   |
| Respiratory rate (/min) | 1.092     | 1.014                   | 1.176   | 0.020   |
| pH                    | 0.030      | 0                       | 19.166  | 0.288   |
| FiO₂ (%)              | 1.006      | 0.977                   | 1.036   | 0.694   |
| PEEP (cmH2O)          | 1.143      | 0.898                   | 1.454   | 0.277   |
| Hct                   | 0.977      | 0.919                   | 1.039   | 0.457   |
| Creatinine            | 0.950      | 0.777                   | 1.162   | 0.620   |
| Albumin               | 0.685      | 0.351                   | 1.337   | 0.268   |
| Weaning status        | 0.388      | 0.156                   | 0.966   | 0.042   |
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Author Contributions

C.M. Chen and K.C. Cheng is the guarantor of this manuscript, C.M. Chao, C.C. Lai, K.S. Chan, and K.C. Cheng contributed to the conception and design of the study, M.I. Sung, A.C. Cheng, and S.C. Hsing analysed and interpreted the data, C.M. Chao, and C.M. Chen drafted the manuscript.

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