Sarcopenia is an effective predictor of difficult-to-wean and mortality among critically ill surgical patients

Hao-Wei Kou\textsuperscript{1}, Chih-Hua Yeh\textsuperscript{2,3}, Hsin-I Tsai\textsuperscript{3,4,5}, Chih-Chieh Hsu\textsuperscript{1}, Yi-Chung Hsieh\textsuperscript{6}, Wei-Ting Chen\textsuperscript{6}, Hao-Tsai Cheng\textsuperscript{3,5,6}, Ming-Chin Yu\textsuperscript{1,3,5,7}, Chao-Wei Lee\textsuperscript{1,3,5,*}

1 Division of General Surgery, Department of Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Guishan, Taoyuan, Taiwan, Republic of China, 2 Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, Linkou Medical Center, Guishan, Taoyuan, Taiwan, Republic of China, 3 College of Medicine, Chang Gung University, Guishan, Taoyuan, Taiwan, Republic of China, 4 Department of Anesthesiology, Chang Gung Memorial Hospital, Linkou Medical Center, Guishan, Taoyuan, Taiwan, Republic of China, 5 Graduate Institute of Clinical Medical Sciences, Chang Gung University, Guishan, Taoyuan, Taiwan, Republic of China, 6 Department of Hepatogastroenterology, Chang Gung Memorial Hospital, Linkou Medical Center, Guishan, Taoyuan, Taiwan, Republic of China, 7 Department of Surgery, Xiamen Chang Gung Hospital, Xiamen, China

☯ These authors contributed equally to this work.

* alanchoweilee@hotmail.com

Abstract

Background

Critically-ill surgical patients are at higher risk for sarcopenia, which is associated with worse survival. Sarcopenia may impair the respiratory musculature, which can subsequently influence the outcome of ventilator weaning. Although there are a variety of weaning parameters predictive of weaning outcomes, none have tried to incorporate “muscle strength” or “sarcopenia”. The aim of the current study was to explore the association between sarcopenia and difficult-to-wean (DtW) in critically-ill surgical patients. The influence of sarcopenia on ICU mortality was also analyzed.

Methods

Ninety-six patients undergoing mechanical ventilation in the surgical intensive care unit (ICU) were enrolled. Demographic data and weaning parameters were recorded from the prospectively collected database, and the total psoas muscle area (TPA) was determined at the level of the 3\textsuperscript{rd} lumbar vertebra by computed tomography. Sarcopenia was defined by previously established cut-off points and its influence on clinical outcomes was examined. Receiver operating characteristic (ROC) curve analysis was conducted to investigate the predictive capability of TPA and weaning parameters for predicting weaning outcomes.

Results

The median age of the studied patients was 73 years. Thirty patients (31.3%) were sarcopenic and 30 (31.3%) were defined as DtW. Eighteen patients (18.8%) had ICU mortality. Multivariate logistic regression analyses revealed that sarcopenia was an independent risk
factor for DtW and ICU mortality. The area under the ROC curve (AUC) of TPA for predicting successful weaning was 0.727 and 0.720 in female and male patients, respectively. After combining TPA and conventional weaning parameters, the AUC for DtW increased from 0.836 to 0.911 and from 0.835 to 0.922 in female and male patients, respectively.

**Conclusion**

Sarcopenia is an independent risk factor for DtW and ICU mortality. TPA has predictive value when assessing weaning outcomes and can be used as an effective adjunct predictor along with conventional weaning parameters.

**Introduction**

In the intensive care unit (ICU), mechanical ventilation should be weaned as early as possible once the clinical condition is stabilized. The decision of whether a patient is ready-to-wean is assessed by various weaning parameters such as the rapid shallow breathing index (RSBI) and several physiological conditions including cardiopulmonary stability [1–4]. Despite favorable weaning profiles, a significant portion of patients, ranging from 10% to 30%, still experience weaning failure or have difficult weaning [5–9]. The pathophysiology of weaning failure is often multifactorial, including comorbidities with dysfunction of the diaphragm/respiratory muscles, lung, and heart [1,2,5]. These patients consume a disproportionate amount of ICU resources [1], are at higher risk of complications such as ventilator-associated pneumonia [10], and more importantly, are associated with increased mortality [6–9,11]. As a result, it is imperative to explore several more effective weaning predictors to improve weaning outcomes.

Sarcopenia is characterized by loss of muscle mass, strength, and function [12,13]. The development of sarcopenia may be related to age, physical activity, nutrition, and diseases such as cancer or chronic inflammation [12,14,15]. Patients with sarcopenia are particularly vulnerable in the presence of major physiologic stressors including major surgery [14] and critical illness [16]. Indeed, in patients who have received major surgery, sarcopenia is associated with poorer outcomes regarding short-term survival, long-term survival, and postsurgical complications [14,17–21]. Likewise, in critically ill patients, sarcopenia is a poor prognostic factor for ventilator-free days, ICU-free days, length of hospital stay, and mortality [15,22–25]. Since sarcopenia may impair the function of respiratory muscles, which in turn influences the weaning process [5,26–29], it is likely that sarcopenia may negatively impact the weaning outcome, especially in surgical patients. However, evidence to support this hypothesis is still lacking. In this retrospective cohort study, we aim to investigate whether sarcopenia is a significant predictive factor for difficult-to-wean (DtW) and ICU mortality in critically ill surgical patients.

**Materials and methods**

**Study population and data collection**

This study was performed in the 10-bed surgical ICU of a 3500-bed tertiary medical center in Taiwan. From November 2013 to November 2014, all patients who had been intubated and mechanically ventilated during their ICU stay were identified. Patients who had unplanned extubation, who were unable to initiate a spontaneous breathing trial (SBT), who did not have available computed tomography images within 30 days of the first SBT, who had a psoas muscle abscess or received lumbar spine surgery, or whose clinical data were not complete were
excluded from our study. A total of 96 patients were eventually enrolled. Their clinical data were retrospectively reviewed from the prospectively collected database. The baseline demographic characteristics, laboratory examinations upon ICU admission, conventional weaning parameters at the first SBT, and total psoas muscle area (TPA) were examined and recorded.

During their ICU stay, weaning was initiated as early as possible. Patients were judged to be ready-to-wean once they fulfilled the criteria, which included 1) a controlled underlying pathology, 2) a stable cardiovascular, metabolic, and mental status, and 3) adequate oxygenation and pulmonary function. The patients regarded as ready-to-wean would undergo a series of SBTs to assess their capability of weaning from the ventilator. The weaning outcome and final survival status were recorded and the patients enrolled were grouped and analyzed accordingly. For internal validation, another 30 patients with identical inclusion/exclusion criteria were randomly selected from the ICU admissions between December 2014 and June 2016.

Definitions

The conventional weaning parameters included tidal volume (VT), respiratory rate (RR), RSBI (determined by RR/VT), maximal inspiratory pressure (Pimax), and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2/FiO2 ratio). During an SBT, the inspiratory pressure of the pressure support ventilation would be reduced to 8 cmH2O or less. Patients who had RR < 30 breaths/min, VT > 5 ml/kg, RSBI < 105, Pimax > -20 cmH2O, or a Pao2/FiO2 ratio > 200 during their SBT were recognized as potential candidates for ventilator independence. Patients were classified as DtW if they required more than 7 days of weaning after the first SBT (i.e., prolonged weaning) or were reintubated within 48 hours of extubation (i.e., weaning failure) [1,5]. For TPA, a specialized radiologist who was blind to the patients’ clinical condition and outcome estimated the psoas muscle mass. We followed a previously described method that measured the cross-sectional area of the psoas muscle at the level of the third lumbar vertebrae. By using a picture archiving and communication system, the psoas muscle area was estimated by multiplying the greatest anterior/posterior and transverse muscle diameters and then normalizing by the patient’s height [mm²/m²] (Fig 1) [30, 31]. The values obtained from this method have been shown to correlate well with those obtained from the image-analysis software package [30]. A TPA less than 385 mm²/m² for female patients or 545 mm²/m² for male patients was defined as sarcopenia [30,31]. Age >75 years was defined as old patient, and operations lasting for more than 5 hours were regarded as prolonged operations.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of the continuous variables. Continuous variables were analyzed by Student’s t-test for normally distributed data and by the Mann–Whitney U test for non-parametrically distributed data, and are presented as the mean ± standard deviation or median with interquartile ranges for the normally and non-parametrically distributed data, respectively. Pearson’s χ² test or Fisher’s exact test was used to compare the categorical variables and was presented as absolute frequency and percentages. Factors that were statistically significant in the univariate analysis were subjected to multivariate logistic regression analysis. The predictive power of individual weaning parameters and various combinations of parameters for weaning outcome was determined by receiver operating characteristic (ROC) curve analysis and was presented as the area under the ROC curve (AUC) [32,33]. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corporation, Software Group, Somers, NY, USA).
Results

Patient characteristics

Table 1 demonstrates the demographic data and clinical outcomes of 96 enrolled patients. The median age was 73 years and most (67.8%) were elderly subjects (age $\geq 65$ years). Among them, 86 (89.6%) patients received abdominal surgery either immediately before or during their ICU admission, with gastrointestinal surgery being the most common type. More than half of these surgical patients (57.0%) underwent oncological surgery. More than one-third of them (36.0%) received emergent surgery and approximately 30% of all recruited patients suffered from sepsis. Table 2 describes the indications for mechanical ventilation for the patients recruited. The most common indication was moderate/severe restrictive lung disease or elderly patients undergoing emergent abdominal operations, followed by elderly patients with mild restrictive lung disease or sepsis with respiratory failure. The median duration of mechanical ventilation was 5 days and the median duration of mechanical ventilation before being ready-to-wean was 3 days. The mean TPA of the entire patient group was 591.7 mm$^2$/m$^2$, and 30 patients (31.3%) were classified as having sarcopenia. Thirty patients (31.3%) were classified as DtW, with 25 suffering from prolonged weaning and 5 suffering from weaning failure. Overall, 18 patients (18.8%) died during their ICU stay. Among these patients, 13 were regarded as DtW; DtW was found to be significantly associated with ICU mortality in the current study (ICU mortality, 43.3% in the DtW group vs. 7.6% in the non-DtW group, $P<0.001$).

Predictors of DtW and ICU mortality

Tables 3 and 4 contain the clinical demographic characteristics, laboratory examinations, and weaning parameters with respect to weaning outcome and ICU mortality. As shown in the tables, DtW patients had significantly lower TPA values and significantly higher acute physiology and chronic health evaluation (APACHE) II scores and sequential organ failure assessment (SOFA) scores than those of non-DtW patients. Patients with sarcopenia, sepsis, and
those undergoing emergent operations were significantly more likely to be DtW patients. Similar results were also observed between ICU survivors and non-survivors. Furthermore, the conventional weaning parameters RR, Vt, and RSBI were found to be significantly associated with the weaning outcome and are comparable to previous studies [2].

Table 5 demonstrates the multivariate logistic regression analysis results for various predictive factors found in the univariate analysis. Sarcopenia (p = 0.038) and APACHE II score (p < 0.001) were found to be independent predictors for DtW, whereas RR < 30 breaths/min (p = 0.044), RSBI < 105 (p = 0.045), and Vt > 5 ml/kg (p = 0.004) were shown to significantly decrease the odds of DtW. On the other hand, sarcopenia (p = 0.042), emergent operation (p = 0.033), and SOFA score (p = 0.004) were independent risk factors for ICU mortality.

Table 1. Demographic characteristics upon ICU admission and clinical outcomes of the study patients.

| Variables                      | Values                                      |
|--------------------------------|---------------------------------------------|
| Age (years)                    | 73.0 (63.0–80.8)                            |
| Sex                            |                                             |
| Male                           | 63 (65.6%)                                  |
| Female                         | 33 (34.4%)                                  |
| Type of surgery                |                                             |
| Hepatectomy                    | 18 (18.8%)                                  |
| Gastrectomy                    | 18 (18.8%)                                  |
| Pancreatic surgery             | 5 (5.2%)                                    |
| GI tract surgery               | 39 (40.6%)                                  |
| Urologic surgery               | 6 (6.3%)                                    |
| Without surgery                | 10 (10.4%)                                  |
| Oncological surgery            |                                             |
| Yes                            | 49 (57.0%)                                  |
| No                             | 37 (43.0%)                                  |
| Emergent surgery               |                                             |
| Yes                            | 31 (36.0%)                                  |
| No                             | 55 (64.0%)                                  |
| Sepsis                         |                                             |
| Yes                            | 28 (29.2%)                                  |
| No                             | 68 (70.8%)                                  |
| APACHE II score                | 16.0 (12.0–20.0)                            |
| SOFA score                     | 5.0 (3.3–8.0)                               |
| BMI (kg/m²)                    | 22.8 (20.5–25.2)                            |
| TPA (mm²/m²)                   | 591.7 ± 212.2                               |
| Male                           | 639.4 ± 28.1                                |
| Female                         | 500.6 ± 33.1                                |
| Sarcopenia                     |                                             |
| Yes                            | 30 (31.3%)                                  |
| No                             | 66 (68.7%)                                  |
| ICU mortality                  |                                             |
| Yes                            | 18 (18.8%)                                  |
| No                             | 78 (81.2%)                                  |
| ICU stay (days)                | 8.5 (4.0–26.8)                              |
| Hospital stay (days)           | 32.5 (23–68.5)                              |
| Difficult-to-wean              |                                             |
| Yes                            | 30 (31.3%)                                  |
| No                             | 66 (68.7%)                                  |
| Duration with MV (days)        | 5 (2.0–22.0)                                |
| MV days before readiness to wean (days) | 3.0 (2.0–7.0) |

ICU, intensive care unit; GI, gastrointestinal; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; BMI, body mass index; TPA, total psoas area; MV, mechanical ventilation. Continuous data are expressed as the mean ± standard deviation or median (interquartile range), and categorical data are expressed as a number (%).

https://doi.org/10.1371/journal.pone.0220699.t001
To predict the occurrence of DtW more accurately, ROC curve analysis of various weaning parameters for weaning outcome was employed. The AUC of TPA alone for predicting successful weaning was 0.727 ± 0.091 in female (Fig 2A) and 0.720 ± 0.071 in male patients (Fig 2B) (Table 6). The AUC of 5 individual conventional weaning parameters (Vt, RR, RSBI, Pimax, and PaO$_2$/FiO$_2$ ratio) for predicting successful weaning or DtW was between 0.688 and 0.752 (Table 6). A logit model of the logistic regression [32,33] incorporating these 5 conventional weaning parameters with and without TPA (WS-5P+TPA and WS-5P, respectively) was established to yield a single weaning score to predict DtW. The AUC was 0.836 ± 0.097 in female patients and 0.835 ± 0.048 in male patients, when WS-5P was adopted. The addition of TPA into the WS-5P model (i.e., WS-5P+TPA) increased the AUC to 0.911 ± 0.075 and 0.922 ± 0.034 in female and male patients, respectively (Fig 2C and 2D, and Table 6).

Internal validation

Among the 30 patients in the validation group, 21 were male, and 9 were female. Eleven patients (36.7%) were classified as having sarcopenia, and 7 patients (23.3%) were defined as DtW. ROC curve analysis was performed to validate the predictive performance of TPA. The AUC of TPA alone for predicting successful weaning was 0.514 in male and 0.944 in female patients. The addition of TPA into the model with 5 conventional weaning parameters (WS-5P+TPA) increased the AUC for predicting DtW from 0.661 to 0.750 in male patients. The AUCs for the WS-5P and WS-5P+TPA models for predicting DtW were both 1.000 in female patients.

Discussion

Critically ill surgical patients, especially those with advanced age [21–23] or cancer [18–20], are at higher risk of sarcopenia. Sarcopenia may impair the function of respiratory muscles
which potentially leads to poor weaning outcomes [5,29]. In the current study, we consecutively enrolled a cohort of critically ill surgical patients from a tertiary medical center in Taiwan. Since more than 80% of our patients underwent abdominal operations, of which nearly 60% were oncological surgery, our patient population was rather homogenous and thus could more accurately allow the investigation of the predictive power of sarcopenia for determining weaning outcomes. The results demonstrated that sarcopenia is a significant predictive factor for DtW among critically ill surgical patients. This finding indicates the importance of skeletal muscle mass or function during ventilator weaning and the necessity of risk stratification prior to the initiation of the weaning process among surgical, especially abdominal surgical, patients.

The current study also noted that among 58 patients whose five conventional weaning parameters were all favorable, 11 patients (19%) were classified as DtW (8 had prolonged weaning, and 3 had weaning failure). This result was comparable to previous studies in which a significant portion of patients are still considered as difficult weaning despite favorable weaning profiles [5–9]. As a result, it is urgently necessary to amend conventional weaning profiles to avoid unnecessary weaning or extubation. After thorough analysis, we discovered from the current study that among these 11 potential weaning candidates, 7 (63.6%) were considered to have sarcopenia. Therefore, we believe that the evaluation of skeletal muscle mass or function should not be neglected and should be incorporated into weaning profiles. Since TPA was found to possess an acceptable discriminative power among successful and non-successful

Table 3. Clinical demographic characteristics of patients, categorized by weaning outcome and ICU mortality, upon ICU admission.

| Variables                | Difficult-to-wean | ICU mortality |
|--------------------------|-------------------|---------------|
|                          | Yes (n = 30)      | No (n = 66)   | P value | Yes (n = 18) | No (n = 78) | P value |
| Age(years)               |                   |               |         |             |             |         |
| ≥65                      | 75.5 (63.8–84.5)  | 72.5 (60.0–80.0) | 0.195 | 67.5 (57.8–77.5) | 74.5 (63.8–81.0) | 0.239 |
| <65                      | 22 (33.8)         | 43 (66.2)     | 0.427 | 10 (15.4)   | 55 (84.6)   | 0.221 |
| Sex                      |                   |               |         |             |             |         |
| Male                     | 19 (30.2)         | 44 (69.8)     | 0.750 | 13 (20.6)   | 50 (79.4)   | 0.513 |
| Female                   | 11 (33.3)         | 22 (66.7)     | 5 (15.2) | 28 (84.8) |             |         |
| BMI (kg/m²)              | 23.8 (20.5–27.6)  | 22.3 (20.5–24.5) | 0.179 | 21.8 (20.5–26.8) | 23.0 (20.5–25.0) | 0.833 |
| BMI classification a     |                   |               |         |             |             |         |
| Underweight              | 5 (41.7)          | 7 (58.3)      | 0.068 | 1 (8.3)     | 11 (91.7)   | 0.092 |
| Normal                   | 8 (21.1)          | 30 (78.9)     | 11 (28.9) | 27 (71.1) |             |         |
| Overweight               | 5 (22.7)          | 17 (77.3)     | 1 (4.5) | 21 (95.5)  |             |         |
| Obese                    | 12 (50.0)         | 12 (50.0)     | 5 (20.8) | 19 (79.2) |             |         |
| Emergent operation b     |                   |               |         |             |             |         |
| Yes                      | 14 (45.2)         | 17 (54.8)     | 0.007 | 9 (29.0)    | 22 (71.0)   | 0.007 |
| No                       | 10 (18.2)         | 45 (81.8)     | 3 (5.5) | 52 (94.5)  |             |         |
| Sepsis                   |                   |               |         |             |             |         |
| Yes                      | 14 (50.0)         | 14 (50.0)     | 0.011 | 9 (32.1)    | 19 (67.9)   | 0.031 |
| No                       | 16 (23.5)         | 52 (76.4)     | 9 (13.2) | 59 (86.8) |             |         |
| TPA (mm²/m²)             | 480.2±188.5       | 642.3±217.6   | 0.001 | 474.6±215.3 | 618.7±215.0 | 0.012 |
| Sarcopenia               |                   |               |         |             |             |         |
| Yes                      | 14 (46.7)         | 16 (53.3)     | 0.028 | 10 (33.3)   | 20 (66.7)   | 0.014 |
| No                       | 16 (24.2)         | 50 (75.8)     | 8 (12.1) | 58 (87.9)  |             |         |

ICU, intensive care unit; TPA, total psoas area; BMI, body mass index. Continuous data are expressed as the mean ± standard deviation or median (interquartile range) and categorical data are expressed as a number (%). P values <0.05 were considered statistically significant.

a Classification according to the World Health Organization Asia-Pacific criteria

b Ten of the study patients did not have an operation during the study period, but they previously (> 1 year) had surgery in this hospital and were cared for in our ICU, mainly for sepsis.

https://doi.org/10.1371/journal.pone.0220699.t003
weaners and the weaning outcome could be improved by combining multiple predictors [34], we decided to incorporate TPA into conventional weaning scores to obtain an even better predictive tool. As shown in the results, the AUC for DtW was further enhanced to 0.911 and 0.922 in female and male patients, respectively, when WS-5P+TPA was adopted. Collectively,

Table 4. Results of the laboratory examination and the weaning profiles of study patients categorized by weaning outcome and ICU mortality.

| Variables                  | Difficult-to-wean | ICU mortality | P value | Difficult-to-wean | ICU mortality | P value |
|----------------------------|------------------|--------------|---------|------------------|--------------|---------|
| Upon admission             |                  |              |         |                  |              |         |
| APACHE II score            | 20.5 (16.8–24.3) | 14.0 (12.0–18.0) | <0.001  | 20.5 (16.0–24.3) | 15.0 (12.0–19.0) | 0.001   |
| SOFA score                 | 7.0 (5.8–10.0)   | 4.0 (3.0–6.5)  | <0.001  | 8.0 (6.0–12.3)   | 5.0 (3.0–7.0)   | <0.001  |
| Creatinine (mg/dl)         | 1.5 (1.0–2.5)    | 0.8 (0.7–1.3)  | 0.003   | 1.3 (0.9–2.6)    | 0.9 (0.7–1.7)   | 0.023   |
| Sodium (mmol/dl)           | 138 (134–142)    | 138 (135–140)  | 0.745   | 135 (130–141)    | 138 (135–141)   | 0.109   |
| Potassium (mmol/dl)        | 3.9 (3.5–4.6)    | 4.0 (3.7–4.5)  | 0.632   | 3.9 (3.5–4.6)    | 4.0 (3.6–4.5)   | 0.728   |
| Albumin (g/dl)             | 2.3 (2.0–2.7)    | 3.1 (2.5–3.5)  | <0.001  | 2.3 (2.0–3.1)    | 2.9 (2.4–3.5)   | 0.005   |
| Hemoglobin                 | 10.9±2.0         | 10.4±1.6      | 0.157   | 10.9±2.0         | 10.4±1.7       | 0.340   |
| Leukocyte count            | 11.7 (8.5–20.9)  | 12.2 (8.7–18.2)| 0.953   | 12.9 (8.7–18.7)  | 11.9 (8.7–18.8)| 0.481   |
| Platelet count             | 175 (92–245)     | 182 (129–281)  | 0.355   | 169 (72–296)     | 182 (132–245)  | 0.551   |

Weaning parameters

| Difficult-to-wean | ICU mortality | P value | Difficult-to-wean | ICU mortality | P value |
|-------------------|--------------|---------|-------------------|--------------|---------|
| RR < 30 vs. >30 breaths/min | 21 (25.9) vs. 9 (60.0) | 0.014   |                   |              |         |
| Vt >5 vs. < 5 ml/kg | 14 (21.9) vs. 16 (50.0) | 0.005   |                   |              |         |
| RSBI <105 vs. >105 | 19 (25.0) vs. 11 (55.0) | 0.010   |                   |              |         |
| Pimax < -20 vs. >-20 cmH2O | 28 (30.1) vs. 2 (66.7) | 0.229   |                   |              |         |
| PaO2/FiO2 ratio>200 vs. <200 | 28 (29.8) vs. 2 (100.0) | 0.095   |                   |              |         |

Table 5. Multivariate logistic regression analysis of independent predictive factors for weaning outcome and ICU mortality.

| Variables                  | Difficult-to-wean | ICU mortality | P value | Difficult-to-wean | ICU mortality | P value |
|----------------------------|------------------|--------------|---------|------------------|--------------|---------|
| Sarcopenia                 | 4.767            | 1.094–20.772 | 0.038   | 5.071            | 1.059–24.277 | 0.042   |
| Emergent operation         |                  |              | NS      |                  |              | NS      |
| Sepsis                     |                  |              | NS      |                  |              | NS      |
| APACHE II score            | 1.440            | 1.201–1.726  | <0.001  |                  |              | NS      |
| SOFA score                 |                  |              | NS      | 1.414            | 1.116–1.791 | 0.004   |
| Creatinine (mg/dl)         |                  |              | NS      |                  |              | NS      |
| Albumin (g/dl)             |                  |              | NS      |                  |              | NS      |
| RR <30 breaths/min         | 0.047            | 0.002–0.918  | 0.044   |                  |              |         |
| Vt >5 ml/kg                | 0.063            | 0.009–0.421  | 0.004   |                  |              |         |
| RSBI <105                  | 0.030            | 0.001–0.923  | 0.045   |                  |              |         |

ICU, intensive care unit; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; RR, respiratory rate; Vt, tidal volume; RSBI, rapid shallow breathing index; OR, odds ratio after adjustment for other confounding factors; CI, confidence interval; NS, no significant difference. P values <0.05 were considered statistically significant.

https://doi.org/10.1371/journal.pone.0220699.t005
we believe that TPA is an important variable during ventilator weaning and should be considered along with conventional weaning parameters to optimize the weaning outcome.

In addition to its negative impact on weaning outcomes, sarcopenia was also identified as an independent risk factor for ICU mortality. The incidence of ICU mortality was also significantly higher in the DtW group than in the non-DtW group. It is likely that the same risk factor, i.e., sarcopenia, impairs the weaning process first and then influences ICU survival. Sarcopenia has been reported to be associated with various adverse outcomes in surgical or critically ill patients. For example, a meta-analysis investigating 24 studies and 5,267 patients indicated that radiologically determined sarcopenia predicted morbidity and mortality following abdominal surgery [17]. Another meta-analysis involving 29 studies and 7,176 patients showed that sarcopenia was associated with an increased risk of postoperative complications in patients with gastrointestinal cancer [19]. Other recent studies also reported that sarcopenia was an independent prognostic factor for complications and survival in either surgical or

Fig 2. Receiver operating characteristic (ROC) curves for various predictors of weaning outcomes in the study patients. TPA represents the total psoas muscle area. Panels A and B show ROC curves predicting successful weaning when TPA alone was used for analysis of female and male patients, respectively. A logit model of the logistic regression incorporating 5 conventional weaning parameters (WS-5P; with respiratory rate, tidal volume, rapid-shallow breathing index, maximum inspiratory pressure, and PaO$_2$/FiO$_2$ ratio as the included weaning parameters) or that model in combination with TPA (WS-5P+TPA) was employed to yield a single weaning score. Panels C and D show ROC curves predicting difficult-to-wean (DtW) when WS-5P and WS-5P+TPA were used for analysis of female and male patients, respectively. The purple line is the reference line.

https://doi.org/10.1371/journal.pone.0220699.g002
Table 6. Area under the receiver operating characteristic (ROC) curves for various predictors of weaning outcomes in the study patients.

| Predictor                  | AUC       | P value | Weaning outcome |
|----------------------------|-----------|---------|-----------------|
| TPA (Female)               | 0.727 ± 0.091 | 0.036   | Success         |
| TPA (Male)                 | 0.720 ± 0.071 | 0.006   | Success         |
| RR                         | 0.700 ± 0.061 | 0.003   | DtW             |
| Vt                         | 0.711 ± 0.058 | 0.001   | Success         |
| RSBI                       | 0.752 ± 0.052 | <0.001  | DtW             |
| Pimax                      | 0.668 ± 0.063 | 0.011   | DtW             |
| PaO2/FiO2 ratio            | 0.732 ± 0.059 | <0.001  | Success         |
| WS-5P (Female)*            | 0.836 ± 0.097 | 0.004   | DtW             |
| WS-5P (Male)*              | 0.865 ± 0.048 | <0.001  | DtW             |
| WS-5+TPA (Female)*         | 0.911 ± 0.075 | <0.001  | DtW             |
| WS-5+TPA (Male)*           | 0.922 ± 0.034 | <0.001  | DtW             |

AUC, area under the ROC curve; DtW, difficult-to-wean; TPA, total psoas area; RR, respiratory rate; Vt, tidal volume; RSBI, rapid shallow breathing index; PiMax, maximum inspiratory pressure; PaO2/FiO2 ratio, the ratio of arterial oxygen partial pressure to fractional inspired oxygen. AUC results are presented as the mean ± standard error (SE). P values <0.05 were considered statistically significant.

* A logit model of the logistic regression incorporating 5 conventional weaning parameters or the same model in combination with TPA (WS-5P or WS-5P+TPA, respectively) was used to determine a single weaning score from the ROC curve analysis.

nonsurgical patients [20–22]. A decrease in skeletal muscle mass as defined by cross-sectional CT imaging has been demonstrated to be a risk factor for in-hospital mortality in ICU patients of old or nonspecific age [23–25]. With the aforementioned evidence, we conclude that TPA or sarcopenia is a rather important parameter in surgical ICUs and should routinely be assessed in critically ill surgical patients.

Since patients in surgical ICUs are usually immobilized or disabled, accurate assessment of their muscle strength is not feasible and a more subjective modality is warranted. It has been suggested that sarcopenia can be assessed by CT imaging techniques in patients in whom measurements of muscle mass, muscle strength, and physical activity are not available [12]. In the current study, we employed CT imaging and a predetermined sex-specific TPA cut-off to estimate TPA and define sarcopenia. The incidence of sarcopenia was comparable to previous studies investigating cancer patients undergoing abdominal surgery (15–50%) and elderly patients suffering from trauma or surgery (24.9–57.5%) [17,21,30,31,35,36]. Since cross-sectional CT imaging is commonly performed in patients scheduled to receive abdominal operations, measurements of TPA are readily available and will not introduce further radiation exposure in this patient subgroup. Therefore, this simple CT imaging technique is a practical and reliable method to assess skeletal muscle mass and sarcopenia in critically ill surgical patients. We do not necessarily require other dedicated computer software, massive calculations, or state-of-the-art instruments to diagnose sarcopenia in this special subgroup of patients.

Despite the remarkable findings, our study still has several limitations. First, the retrospective nature of the current study renders selection bias and missing data inevitable. Second, the size of the validation group is rather small, resulting in less significant results. Third, the current study lacks external validation to support our findings. Future prospective investigations with a larger sample size and external validation group are warranted to validate our findings.

Conclusions

In conclusion, our study demonstrates that sarcopenia is an independent risk factor for DtW and ICU mortality in critically ill surgical patients. TPA has prognostic significance in
predicting weaning outcomes and should be considered along with other conventional weaning parameters in surgical ICUs. Further studies are necessary to confirm our findings.

**Supporting information**

S1 Dataset. Minimal anonymized dataset necessary to replicate the study finding. (XLS)

**Acknowledgments**

We are grateful to all our colleagues in the GS ICU 1, Department of Surgery, Chang Gung Memorial Hospital, and the Graduate Institute of Clinical Medical Sciences, Chang Gung University for their technical assistance. We are also grateful to Jo-Chu Chiu and Yi-Ping Liu for their assistance in data retrieval and processing.

**Author Contributions**

- **Conceptualization:** Wei-Ting Chen, Chao-Wei Lee.
- **Data curation:** Chih-Chieh Hsu, Yi-Chung Hsieh.
- **Formal analysis:** Hao-Wei Kou, Chih-Hua Yeh.
- **Funding acquisition:** Ming-Chin Yu, Chao-Wei Lee.
- **Investigation:** Hsin-I Tsai, Chih-Chieh Hsu.
- **Methodology:** Yi-Chung Hsieh, Hao-Tsai Cheng.
- **Project administration:** Chao-Wei Lee.
- **Resources:** Wei-Ting Chen, Hao-Tsai Cheng.
- **Software:** Chih-Hua Yeh.
- **Supervision:** Chao-Wei Lee.
- **Validation:** Hsin-I Tsai, Ming-Chin Yu.
- **Writing – original draft:** Hao-Wei Kou.
- **Writing – review & editing:** Hsin-I Tsai, Ming-Chin Yu, Chao-Wei Lee.

**References**

1. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, et al. Weaning from mechanical ventilation. Eur Respir J. 2007 May; 29(5):1033–56. https://doi.org/10.1183/09031936.00010206 PMID: 17470624
2. Baptistella AR, Sarmento FJ, da Silva KR, Baptistella SF, Taglietti M, Zuquello RA, et al. Predictive factors of weaning from mechanical ventilation and extubation outcome: A systematic review. J Crit Care. 2018 Dec; 48:56–62. https://doi.org/10.1016/j.jcrc.2018.08.023 PMID: 30172034
3. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. N Engl J Med. 1991 May 23; 324(21):1445–50. https://doi.org/10.1056/NEJM199105233242101 PMID: 2023603
4. Capdevila XJ, Perrigault PF, Perery PJ, Roustan JP, d’Athis F. Occlusion pressure and its ratio to maximum inspiratory pressure are useful predictors for successful extubation following T-piece weaning trial. Chest. 1995 Aug; 108(2):482–8. https://doi.org/10.1378/chest.108.2.482 PMID: 7634888
5. Heunks LM, van der Hoeven JG. Clinical review: the ABC of weaning failure—a structured approach. Crit Care. 2010; 14(6):245. https://doi.org/10.1186/cc9296 PMID: 21143773
6. Jeong BH, Ko MG, Nam J, Yoo H, Chung CR, Suh GY, et al. Differences in clinical outcomes according to weaning classifications in medical intensive care units. PLoS One. 2015 Apr 15; 10(4):e0122810. https://doi.org/10.1371/journal.pone.0122810 PMID: 25876004
7. Pu L, Zhu B, Jiang L, Du B, Zhu X, Li A, et al. Weaning critically ill patients from mechanical ventilation: A prospective cohort study. J Crit Care. 2015 Aug; 30(4):862.e7–13.

8. Funk GC, Anders S, Breyer MK, Burghuber OC, Edelmann G, Heinl W, et al. Incidence and outcome of weaning from mechanical ventilation according to new categories. Eur Respir J. 2010 Jan; 35(1):88–94. https://doi.org/10.1183/09031936.00056909 PMID: 19541716

9. Béduneau G, Pham T, Schortgen F, Piquillon L, Zoghbi E, Jonas M, et al; WIND (Weaning according to a New Definition) Study Group and the REVA (Réseau Européen de Recherche en Ventilation Artificielle) Network. Epidemiology of Weaning Outcome according to a New Definition. The WIND Study. Am J Respir Crit Care Med. 2017 Mar 15; 195(6):772–783. https://doi.org/10.1164/rccm.201602-0320OC PMID: 27626706

10. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med. 2000 May; 161(5):1530–6. https://doi.org/10.1164/ajcc.161.5.9905102 PMID: 10806150

11. Damuth E, Mitchell JA, Bartock JL, Roberts BW, Trzeciak S. Long-term survival of critically ill patients treated with prolonged mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015 Jul; 3(7):544–53. https://doi.org/10.1016/S2213-2600(15)00150-2 PMID: 26003390

12. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, et al; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010 Jul; 39(4):412–23. https://doi.org/10.1093/ageing/afq034 PMID: 20392703

13. Fuggle N, Shaw S, Dennison E, Cooper C. Sarcopenia. Best Pract Res Clin Rheumatol. 2017 Apr; 31(2):218–242. https://doi.org/10.1016/berh.2017.11.007 PMID: 29242498

14. Friedman J, Lussiez A, Sullivan J, Wang S, Englesbe M. Implications of sarcopenia in major surgery. J Am Coll Surg. 2015 Sep; 221(6):1020–32. https://doi.org/10.1016/j.jamcollsurg.2015.08.013 PMID: 26216930

15. Burton LA, Sumukadas D. Optimal management of sarcopenia. Clin Interv Aging. 2010 Sep 7; 5:217–28. PMID: 20852669

16. Kızıllarslanoğlu MC, Kuyumcu ME, Yesil Y, Halli M. Sarcopenia in critically ill patients. J Anesth. 2015 Mar; 29(1):107–11. https://doi.org/10.1007/s00540-015-1784-7 PMID: 25661482

17. Simonsen C, de Heer P, Bjerre ED, Suetta C, Hojman P, Pedersen BK, et al. Sarcopenia and Postoperative Complications in Gastrointestinal Surgical Oncology: A Meta-analysis. Ann Surg. 2015 Oct; 262(1):58–69. https://doi.org/10.1097/SLA.0000000000002361 PMID: 29373365

18. Joglekar S, Nau PN, Mezhrir JJ. The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature. J Surg Oncol. 2015 Oct; 112(5):503–9. https://doi.org/10.1002/jso.24025 PMID: 26310812

19. Rangel EL, Rios-Diaz AJ, Uyeda JW, Castillo-Angeles M, Cooper Z, Olufoja OA, et al. Sarcopenia increases risk of long-term mortality in elderly patients undergoing emergency abdominal surgery. J Trauma Acute Care Surg. 2017 Dec; 83(6):1179–1186. https://doi.org/10.1097/TA.0000000000001657 PMID: 28777289

20. Toptas M, Yalcin M, Akkoç I, Demir E, Metin C, Savas Y, et al. The Relation between Sarcopenia and Mortality in Patients at Intensive Care Unit. Biomed Res Int. 2018 Feb 12; 2018:5263208. https://doi.org/10.1155/2018/5263208 PMID: 29789798

21. Moisey LL, Mourtzakis M, Cotton BA, Premji T, Heyland DK, Wade CE, et al; Nutrition and Rehabilitation Investigators Consortium (NUTRIC). Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. Crit Care. 2013 Sep 19; 17(5):R206. https://doi.org/10.1186/cc12901 PMID: 24050662

22. Shibahashi K, Sugiyama K, Kashiura M, Hamabe Y. Decreasing skeletal muscle mass as a risk factor for mortality in elderly patients with sepsis: a retrospective cohort study. J Intensive Care. 2014 Jan 13; 1(2):R2. https://doi.org/10.1186/2050-2313-1-2 PMID: 24418683

23. Elliott JE, Greising SM, Mantilla CB, Siek GC. Functional impact of sarcopenia in respiratory muscles. Respir Physiol Neurobiol. 2016 Jun; 226:137–46. https://doi.org/10.1016/j.resp.2015.10.001 PMID: 26467183
27. Izawa KP, Watanabe S, Oka K, Kasahara Y, Morio Y, Hiraki K, et al. Respiratory muscle strength in relation to sarcopenia in elderly cardiac patients. Aging Clin Exp Res. 2016 Dec; 28(6):1143–1148. https://doi.org/10.1007/s40520-016-0534-5 PMID: 26802002

28. Kim J, Davenport P, Sapienza C. Effect of expiratory muscle strength training on elderly cough function. Arch Gerontol Geriatr. 2009 May-Jun; 48(3):361–6. https://doi.org/10.1016/j.archger.2008.03.006 PMID: 18457885

29. Magalhães PAF, Camillo CA, Langer D, Andrade LB, Duarte MDCMB, Gosselink R. Weaning failure and respiratory muscle function: What has been done and what can be improved? Respir Med. 2018 Jan; 134:54–61. https://doi.org/10.1016/j.rmed.2017.11.023 PMID: 29413508

30. Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. Colorectal Dis. 2015 Jan; 17(1):O20–6. https://doi.org/10.1111/ced.12805 PMID: 25328119

31. Mirkin KA, Luke FE, Gangi A, Pimienta JM, Jeong D, Hollenbeck CS, et al. Sarcopenia related to neoadjuvant chemotherapy and perioperative outcomes in resected gastric cancer: a multi-institutional analysis. J Gastrointest Oncol. 2017 Jun; 8(3):589–595. https://doi.org/10.21037/jgo.2017.03.02 PMID: 28736646

32. Sturmer T, Joshi M, Glynn RJ, Avorn J, Rothman KJ, Schneeweiss S. A review of the application of propensity score methods yielded increasing use, advantages in specific settings, but not substantially different estimates compared with conventional multivariable methods. J Clin Epidemiol. 2006; 59(5):437–447. https://doi.org/10.1016/j.jclinepi.2005.07.004 PMID: 16632131

33. Croce MA, Tolley EA, Fabian TC. A formula for prediction of posttraumatic pneumonia based on early anatomic and physiologic parameters. J Trauma. 2003 Apr; 54(4):724–9 https://doi.org/10.1097/01.TA.0000054643.54218.C5 PMID: 12707535

34. Nemer SN, Barbas CS, Caldeira JB, Carías TC, Santos RG, Almeida LC, et al. A new integrative weaning index of discontinuation from mechanical ventilation. Crit Care. 2009; 13(5):R152. https://doi.org/10.1186/cc8051 PMID: 19772625

35. Leeper CM, Lin E, Hoffman M, Fombona A, Zhou T, Kutcher M, et al. Computed tomography abbreviated assessment of sarcopenia following trauma: The CAASST measurement predicts 6-month mortality in older adult trauma patients. J Trauma Acute Care Surg. 2016 May; 80(5):805–11. https://doi.org/10.1097/TA.0000000000000989 PMID: 26885997

36. McCusker A, Khan M, Kulvatunyou N, Zeeshan M, Sakran JV, Hayek H, et al. Sarcopenia defined by a computed tomography estimate of the psoas muscle area does not predict frailty in geriatric trauma patients. Am J Surg. 2018 Aug 3.