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ICU ACQUIRED WEAKNESS IN PATIENTS WITH RESPIRATORY FAILURE

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Background: *Most patients with severe respiratory failure in intensive care unit (ICU) require bed rest. The limitation of physical activity leads to some adverse consequences such as ICU Acquired Weakness (ICUAW). Progression of respiratory failure, including that caused by the new coronavirus infection (COVID-19), can lead to the development of acute respiratory distress syndrome, the treatment of which contributes to a combination of risk factors for the development of ICUAW. Traditional diagnostic methods have certain limitations. Muscle ultrasonography is a modern tool for early detection of muscle mass loss.* ***Aims:*** *To compare different methods of early ICUAW screening and to estimate the incidence and peculiarities of ICUAW in patients with respiratory failure of infectious genesis.* ***Methods:*** *31 patients with severe coronavirus pneumonia (COVID-19 "+") and 13 patients with viral and/or bacterial lung infection (COVID-19 "-") were included in the study. The muscle mass loss percent from day 1 to day 7 was higher in the COVID-19 "-" group (p=0.022). These patients also had longer durations of the ICU and hospital stay but a significantly lower mortality (2.5 times).* ***Results:*** *The analysis of the parameters of deceased and living patients regardless of the lung damage etiology showed a correlation between the indices of hand grip strength dynamometry (handgrip test) and ultrasonography of the thigh muscles: F1 and D1 (rho=0.6, p=0.003), F1 and S1 (rho=0.6, p=0.005), D1 and F7 (rho=0.9, p=0.001). In addition, the examined levels of the ICUAW markers were associated with age - F1 (rho=-0.6, p=0.001), D1 (rho=-0.4, p=0.003), S1 (rho=-0.4, p=0.004).* ***Conclusions:*** *During the critical illness, ICUAW develops by the 3d day of bed rest in two thirds of patients with respiratory failure of different infectious genesis. The correlation between the investigated markers of ICUAW and age indicates that elderly patients are the most vulnerable category in respect to the formation and progression of muscle weakness in the ICU. The handgrip test can serve as a reliable and simple method of ICUAW screening. Early identification of patients with ICUAW should provide the improvement of nutritional support and individualization of rehabilitation.*

Keywords: *respiratory failure; ultrasound; dynamometry; muscle weakness; ICU; COVID-19.*

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BACKGROUND

Respiratory failure is the most common causes of hospitalization of patients in the resuscitation and intensive care unit (ICU) [1, 2]. Most patients with severe respiratory failure require bed rest in the ICU. One of the negative consequences of such a limitation of motor activity is the syndrome of weakness acquired in the ICU (SWAI), manifested by hypodynamia, generalized symmetric weakness of the respiratory muscles and muscles of the extremities, and complicating the liberation of patients from artificial pulmonary ventilation [3, 4]. The progression of this syndrome can lead to a loss of one third of muscle mass in critically ill patients [5]. SWAI is based on the so-called polymioneuropathy of critical conditions, characterized by primary axonal degeneration without demyelination, described back in the 1980s [6].

The prevalence of SWAI varies widely depending on the patient population under study, the presence of risk factors, time and diagnostic methods. The main predictors of the syndrome development are old age, female gender, weight deficit, concomitant diseases, multiple organ failure, hyperglycemia, the use of drug sedation, glucocorticosteroids, and muscle relaxants [7, 8]. The frequent combination of such factors in the treatment of patients with a new coronavirus infection (COVID-19) makes this group of patients the most vulnerable to the development of SWAI.

Electromyography is the gold standard for diagnosing SWAI [3], but the technique is not widely available and does not detect all forms of pathological condition [4], therefore the diagnosis is traditionally established clinically using the Medical Research Council (MRC) scale. Nevertheless, certain limitations often registered in ICU patients (impairment and confusion of consciousness, encephalopathy, sedation, paresis) complicate the use of MRC in critically ill patients [9]. Muscle ultrasonography is a contemporary, safe, inexpensive and effective bedside tool for early detection of muscle loss. The reliability and reproducibility of this technique has been demonstrated in a number of studies [10].

Computed tomography and magnetic resonance imaging provide more detailed visualization of muscle infiltration by adipose tissue and determination of the volume of lean muscle mass, however, the disadvantages of these technologies (high cost, the need for specialized software, radiation exposure and the complexity of logistics of patients in critical condition) prevent their routine use [11].

A potential early biomarker of muscle tissue degradation and the risk of SWAI development may be the ratio of plasma levels of urea and creatinine (UCR) [12]. The possibility of routine use of this indicator in follow-up from the first days of admission to the ICU distinguishes it favorably from other diagnostic methods which as a rule reveal the final stages of muscle manifestations of the syndrome of the intensive care after-effects.

Despite the experience accumulated by specialists, the diagnostic value of various methods for assessing muscle mass, as well as its relationship with muscle strength in patients with respiratory failure, remains unclear.

The study aimed to compare various methods of early screening of SWAI, to assess the incidence and aspects of this syndrome in patients with respiratory failure of an infectious origin.

METHODS

Study design

Single-center prospective longitudinal study.

Inclusion criteria

The inclusion criterion was the presence of respiratory failure in the patient requiring oxygen therapy. Patients with a short course of ICU treatment (less than 7 days) were excluded from the study.

Study conditions

The study was conducted in the ICU of the Federal Clinical Research Centre of the Federal Medical Biological Agency of Russia (Moscow).

Study duration

The study was conducted from 2019 to 2021.

Description of the medical intervention

44 patients with diagnoses of pneumonia and chronic obstructive pulmonary disease were examined. The study group (COVID-19 "+") included 31 patients with severe COVID-19; 13 patients with viral and/or bacterial pulmonary infection (community-acquired viral pneumonia, nosocomial pneumonia, exacerbation of chronic obstructive pulmonary disease) were included in the control group (COVID-19 "–").

The infectious genesis of lung damage was verified using computed tomography, polymerase chain reaction (for SARS-CoV-2 and H1N1 viruses), as well as bacteriological monitoring. Hematological and biochemical parameters (levels of hemoglobin, lymphocytes, creatinine, urea, albumin, and C-reactive protein), M. Charlson comorbidity index (CCI), as well as the number of points on the scales of organ dysfunction assessment SOFA (Sequential Organ Failure Assessment) and the severity of the patients' condition APACHE II (Acute Physiology and Chronic Health Evaluation II score) was assessed before the start of the study.

The muscles were imaged with the patient's supine position, using an ultrasound machine with a 1–5 MHz convex probe (CX50, Koninklijke Philips NV, Netherlands) perpendicular to the long axis of the limb by measuring the thickness (D) and cross-sectional area (S) of the right rectus femoris. The measurement point was the midpoint of the distance between the lateral femoral condyle and the greater trochanter. In COVID-19 patients, to assess the muscle strength (F), dynamometry indicators were additionally recorded using a hand dynamometer (DMER-120-0.5, Russia). Ultrasonography and muscle dynamometry were performed sequentially by the same specialist on days 1, 3, and 7. The results at each time point were registered by calculating the arithmetic mean of three measurements. The change in thickness (ΔD_{1-7}) and cross-sectional area (ΔS_{1-7}), expressed as a per-

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centage, was calculated as the ratio of the difference between the values measured on the days 1 and 7 to the values on the day 1 multiplied by 100.

Nutritional support was provided to all patients in the amount of 20–25 kcal/kg per day through clinical (enteral or parenteral) nutrition.

Study outcomes

The main study outcome consisted in assessment of the frequency of decrease in muscle mass and strength by the day 3 of ICU stay in patients with respiratory failure of various infectious genesis.

Additional study outcomes consisted in comparison of the indicators of the early screening methods used for SWAI in surviving and deceased patients, as well as an assessment of the relationship between the measured parameters and the main predictors of mortality in ICU patients.

Ethical considerations

The study protocol and informed consent form were approved by the local ethics committee (protocol No. 3 dated 08/08/2019).

Statistical analysis

Statistical analysis was performed using the SPSS software (version 23, IBM, USA). The data were presented as median (25–75th percentile). Intergroup comparisons were performed using the Mann-Whitney U-test or the χ^2 test. Spearman's rank correlation coefficient (rho) was used to assess correlations. A two-tailed *p*-value lower than 0.05 was considered statistically significant.

RESULTS

Key research results

There were no statistically significant differences between the groups in terms of baseline demographic indicators, severity of the condition and comorbidity, however the degree of organ failure was higher in the COVID-19 "-" group (Table 1). In patients of the same group, in the complex of treatment, artificial pulmonary ventilation was used more often, but glucocorticosteroid therapy was used less often. Patients in both groups had a high incidence of persistent hyperglycemia. As a result of this combination of risk factors for SWAI with forced hypodyna-

Table 1

Comparison of the main manifestations, causes and consequences of ICUAW in patients with respiratory failure of various infectious genesis

Parameters	COVID-19 «+» *n*=31	COVID-19 «-» *n*=13	*p*
Age, years	71 (60–81)	66 (59–77)	0,368
Gender, men/women	17/14	9/4	0,376
APACHE II, score	18 (14–20)	18 (13–23)	0,857
SOFA, score	4 (2–6)	7 (3–9)	0,033*
CCI, score	4 (3–6)	6 (2–7)	0,248
D_1, cm	1,4 (1,3–1,7)	1,5 (1,3–2,0)	0,543
S_1, cm^2	8,6 (6,7–10,4)	7,5 (4,3–9,5)	0,203
Frequency of decrease in muscle strength by the day 3, %	64,3	-	-
Frequency of muscle mass decrease by day 3, %	65,2	76,9	0,464
ΔD_{1-7}, %	0,0 (-11,9–11,9)	6,9 (1,3–21,1)	0,205
ΔS_{1-7}, %	6,5 (-0,1–13,1)	20,5 (13,3–33,5)	0,022*
Artificial pulmonary ventilation frequency, %	61,3	100	0,009*
Glucocorticosteroid therapy frequency, %	100	23,1	<0,001*
Frequency of hyperglycemia >10 mmol/L, %	87,1	92,3	0,187
Bed-days in ICU, days	7 (4–11)	33 (14–49)	<0,001*
Bed-days in the clinic, days	19 (13–24)	45 (21–55)	0,002*
Mortality, %	58,1	23,1	0,034*

Note. * p <0.05. ОРИТ — intensive care unit; СПОС — Intensive Care Unit Acquired Weakness (ICUAW); ИВЛ — mechanical ventilation; ГКС — glucocorticosteroids; APACHE II — Acute Physiology and Chronic Health Evaluation II score ; SOFA — Sequential Organ Failure Assessment ; CCI — M. Charlson comorbidity index; D_1 — thickness of the rectus femoris muscle on day 1; S_1 — cross-sectional area of the rectus femoris muscle on day 1; ΔD_{1-7} — change in the thickness of the rectus femoris muscle from day 1 to 7; ΔS_{1-7} — change in the cross-sectional area of the rectus femoris from day 1 to 7.

mia, already by the day 3, the frequency of muscle mass decrease (thickness and/or cross-sectional area of the rectus femoris muscle) was 65.2% in the COVID-19 "+" group and 76.9% in the COVID-19 "-" group (p = 0.464). It is noteworthy that in the group of COVID-19 patients, where dynamometry indicators were additionally recorded, the frequency of decrease in muscle strength and muscle mass by the day 3 almost coincided (64.3% and 65.2%, respectively). The percentage of muscle mass decrease from the day 1 to the day 7 was higher in the COVID-19 "-" group (p = 0.022). These patients also had a longer duration of treatment, but significantly less (2.5 times) mortality rate.

Additional research results

We also analyzed the clinical and demographic indicators of surviving and deceased patients regardless of the etiology of lung lesions (Table 2).

The deceased patients were older and initially had higher levels of severity of the condition and the degree of organ failure. With an equal body mass index, the deceased patients had lower muscle mass at baseline than the survivors, although the differences were not statistically significant.

Correlation analysis confirmed the relationship between the indicators of handgrip test and ultrasonography of the thigh muscles, namely F_1 and D_1 (rho = 0.6, p = 0.003), F_1 and S_1 (rho = 0.6, p = 0.005), D_1 and F_7 (rho = 0.9, p = 0.001). The relationship between the thickness and cross-sectional area of the rectus femoris muscle persisted throughout the follow-up period, namely D_1 and S_1 (rho = 0.8, $p \leq 0.001$), D_3 and S_3 (rho = 0.8, $p \leq 0.001$), D_7 and S_7 (rho = 0.6, p = 0.001). In addition, the levels of the SWAI markers studied were associated with age, namely F_1 (rho = -0.6, p = 0.001), D_1 (rho = -0.4, p = 0.003), S_1 (rho = -0.4, p = 0.004), UCR_1 (rho = 0.4, p = 0.005), and comorbidity index,

Table 2

Clinical and demographic characteristics of surviving and deceased patients

Parameter	Survivors *n*=23	Deceased *n*=21	*p*
Age, years	64 (59–77)	76 (67–82)	0,024*
Gender, men/women	14/9	12/9	0,802
APACHE II, score	14 (13–19)	19 (17–23)	0,001*
SOFA, score	3 (2–7)	6 (3–7)	0,107
BMI, kg/m²	32 (28–36)	32 (26–35)	0,813
CCI, score	4 (2–6)	5 (3–7)	0,302
Hemoglobin, g/l	127 (112–145)	140 (120–151)	0,404
Lymphocytes, ×10⁹/l	0,81 (0,42–1,06)	0,64 (0,39–1,15)	0,859
Albumin, g/l	31 (30–34)	31 (29–34)	0,979
Serum level of C-reactive protein, mg/l	64 (11–162)	26 (13–76)	0,285
D_1, cm	1,5 (1,4–1,9)	1,4 (1,3–1,6)	0,064
S_1, cm²	8,5 (6,7–10,4)	7,4 (5,8–9,4)	0,384
D_7, cm	1,4 (1,2–1,7)	1,5 (1,3–1,5)	0,609
S_7, cm²	6,3 (4,7–8,1)	6,7 (6,4–9,9)	0,344
F_1, daN	28,2 (17,3–44,7)	31,0 (19,2–48,2)	0,740
UCR_3, mmol/l	124 (96–152)	155 (131–189)	0,014*
Bed-days in the clinic, days	22 (19–43)	17 (10–24)	0,015*
Bed-days in ICU, days	8 (7–22)	9 (7–19)	0,860

Note. * p <0.05. ИМТ — body mass index; OMK_3 — urea-to-creatinine ratio on day 3; APACHE II — Acute Physiology and Chronic Health Evaluation II SCORE ; SOFA — Sequential Organ Failure Assessment ; CCI — M. Charlson comorbidity index; ОРИТ — intensive care unit; D_1 — thickness of the rectus femoris muscle on day 1; S_1 — cross-sectional area of the rectus femoris muscle on day 1; F_1 — muscle strength on day 1; ΔD_{1-7} — change in the thickness of the rectus femoris muscle from day 1 to 7; ΔS_{1-7} — change in the cross-sectional area of the rectus femoris muscle from day 1 to 7.

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namely F_1 (rho = -0.5, p = 0.010), and S_1 (rho = -0.3, p = 0.034).

DISCUSSION

Our data indicate that neuromuscular manifestations of the syndrome of the consequences of intensive care in patients with respiratory failure are already formed by the day 3 of the critical state and represent a frequent complication of forced bed rest. Comprehensive dynamic assessment of dynamometry indicators, muscle ultrasonography and UCR can be used as a simple, non-invasive and inexpensive alternative to the classical methods of SWAI screening in ICU patients.

The incidence of muscle weakness with long-term ICU treatment can be as high as 100% [13, 14], and there is growing scientific evidence that muscle loss is associated with outcomes in critically ill patients [16, 17]. However, a number of authors associate increased mortality rate in debilitated ICU patients not with a decrease in muscle mass as such, but with an increased comorbidity of such patients [18].

We also revealed a relationship between muscle strength and cross-sectional area with the comorbidity index, however, the associations identified should be interpreted with caution, since one of the main indicators in calculating the CCI is age. Indeed, the levels of all the SWAI markers studied by us were associated with age. In addition, the incidence of sarcopenia, which is often a pre-existing myodegenerative disease, increases with age, which manifestations can be aggravated after hospitalization in the ICU [19]. K. Rustani et al. [20] even suggested a cut-off point of 0.7 cm for women and 0.9 cm for men as a threshold value for measuring the thickness of the rectus femoris to detect sarcopenia by ultrasonography. Similar normal limits have been described for dynamometric screening of sarcopenia [21]. The objectives of our study did not include detection of sarcopenia as a separate disease at the prehospital stage. We assumed that the principles of treating muscle weakness in ICU patients are similar regardless of its etiology [22]. Limiting muscle loss during critical illness can improve short-term and possibly long-term treatment outcomes, although chronic sarcopenia is very difficult to reverse [23]. Nevertheless, the general approach in the treatment of muscle weakness in ICU patients is the optimization of muscle load, namely prevention of muscle inactivity (early mobilization, myostimulation) and their excessive tension (adequate pain control), metabolic support (early enteral nutrition, correction of glycemic and electrolyte disorders), as well as potential pharmacotherapy (adequate replenishment of vitamins and nutrients) [24].

Special attention should be paid to patients with respiratory failure due to the severe and extremely severe course of COVID-19. P.A. Lönnqvist et al. [25] suggested an increased frequency of SWAI in this cohort of patients. Our data did not support this hypothesis, although the percentage of patients with muscle weakness was comparable to that revealed by the colleagues [26]. The combination of these results with a higher mortality rate in the group of COVID-19 patients in our study, despite the lower frequency of artificial pulmonary ventilation and the severity of organ failure, demonstrates the features of coronavirus infection. In addition, in COVID-19 patients, standard laboratory parameters such as albumin and lymphocyte counts are not indicators of nutritional deficiency, since they are involved in the inflammatory process [27]. This fact underlines the importance of using alternative methods for assessing nutritional status. The efficiency of muscle ultrasonography for this purpose has been demonstrated in a number of pathologies [28].

Study limitations

Our study was limited by a small sample size and single center design. We also excluded patients with a short duration of treatment, which may have influenced the final results. We did not use indirect calorimetry due to increased risk of infection of patients through the metabolimeter and the increased workload on the medical staff, but, undoubtedly, the changes over time of muscle mass and strength values in a particular patient, taking into account the basal metabolic rate, would be more significant. We also did not assess the relationship between the progression of SWAI and the time and volume of rehabilitation performed, since in a pandemic, taking into account the condition severity of most patients, their regular mobilization was difficult.

CONCLUSION

During a critical condition, in 2/3 of patients with respiratory failure of various infectious genesis, SWAI is formed by the day 3 of bed rest. This confirms the need for widespread introduction of screening for neuromuscular manifestations of the intensive care after-effects syndrome. The revealed interrelation of all the studied SWAI markers with age indicates the greatest vulnerability of elderly patients to the formation and progression of muscle weakness in the ICU. Age-related muscle involution can be manifested not only by a decrease in their strength, thickness, and volume, but also by an early increase in UCR as a marker of muscle tissue degradation. However, this indicator is nonspecific, and the diagnostic value of its isolated use is extremely low.

The high correlation of the strength of the forearm muscles with the thickness and cross-sectional area of the musculus rectus femoris demonstrates that handgrip test can serve as a reliable and simple method for screening the state of the muscular system, which is not inferior in terms of information content to more complex measurements of strength and mass of various muscle groups.

Thus, muscle dynamometry and ultrasonography can be useful in detecting muscle weakness in critically ill patients when traditional screening methods are difficult to apply. Early identification of SWAI patients will help optimize nutritional support and individualization of rehabilitation programs.

ADDITIONAL INFORMATION

Author contribution. Andreychenko S.A. — the study concept and design, statistical analysis of the data, material collection and processing, manuscript writing; Bychinin M.V. — the study concept and design, manuscript editing and approval for publication; Korshunov D.I. — material collection and processing; Klypa T.V. — manuscript editing and approval for publication. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declare that they have no competing interests.

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