ORIGINAL ARTICLE

Intensive Care Unit-acquired Neuromuscular Weakness: A Prospective Study on Incidence, Clinical Course, and Outcomes

Skaria Baby[1], Christina George[2], Narjeet M Osahan[3]

Abstract

Background: Neuromuscular weakness may manifest subsequent to critical illness in intensive care unit (ICU) patients. This weakness termed as "ICU-acquired weakness" (ICUAW) has a significant bearing on the length of mechanical ventilation, duration of ICU stays, long-term disability, and survival rate. Early identification of ICUAW helps in planning appropriate strategies, as well as in predicting the prognosis and long-term outcomes of these patients.

Aims and objectives: To identify the incidence of new-onset neuromuscular weakness developing among patients admitted in the ICU (ICUAW) and study its clinical course and impact on the duration of ICU stay.

Methods: This prospective observational study evaluated patients admitted to the ICU over a period of 1 year and 3 months (November 1, 2015, to January 31, 2017). All patients fulfilling the inclusion and exclusion criteria were evaluated with the Medical Research Council (MRC) score for muscle strength. Patients with an average score <4 were diagnosed with ICUAW. Included patients were examined on alternate days to study the clinical progression of the weakness till ICU discharge or death of the patient. The duration of ICU stay was noted.

Results and conclusion: The study revealed a significant association of ICUAW with age, Acute Physiology And Chronic Health Evaluation (APACHE II) Score, duration of mechanical ventilation, and ICU mortality. The incidence of the weakness was found to be 7.83% among the patients who survived and 50% among those patients who did not survive critical illness.

Keywords: Intensive care unit, Medical Research Council score, Neuromuscular weakness.

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Introduction

It is known for a long that severe illness causes muscle weakness and muscle atrophy.[1] Intensive care unit (ICU)-acquired neuromuscular weakness is a much under-appreciated critical care diagnosis around the world. One cannot overemphasize the harm resulting from ICU-acquired neuromuscular dysfunction given that the compromised functionality and quality of life in ICU survivors have been associated with persistent pain,[2–4] contractures,[5] and muscle weakness.[6] The significance of ICU-acquired weakness (ICUAW) for caregivers outside scales up as the ICU survival rates improve. The ambiguity around the issue is so much that there has been no global consensus among the experts on the diagnosis and treatment of this condition. This is despite the finding that the incidence observed of ICUAW ranges from 25 to 100%.[7,8] An early diagnosis and management of ICUAW helps in avoiding unnecessary investigations for evaluating motor neurological manifestations of the same, for better prognostication, and also in reducing the number of days of ICU stay. This translates to better utilization of resources and reducing the number of disease-adjusted life years (DALYs) lost. Added to that is the psychological, emotional, and financial burden of the caregivers at home.

However, a renewed attention has been given to ICU-acquired neuromuscular weakness over the last three decades. The term ICUAW is used to designate clinically confirmed weakness in patients with critical illness, for whom there is no justifiable reason other than critical illness, for their neuromuscular weakness.[1] ICUAW can be broadly classified as:

- Critical illness polyneuropathy
- Critical illness myopathy
  - Cachectic myopathy
  - Thick-filament myopathy
  - Necrotizing myopathy
- Critical illness neuromyopathy

Various study groups have found out that the three types of ICUAW coexist in most of the patients who were diagnosed to have developed this condition.[7,9–11]

Several predisposing factors identified till date include the age of the patient,[12,13] female gender,[7] long-term use of steroids, neuromuscular blocking agents, aminoglycoside antibiotics, poor glycemic control,[14,15] sepsis,[16,17] bacteremia,[18,19] Systemic Inflammatory Response Syndrome (SIRS),[8,20] and Multiple Organ Failure (MOF).[7] The chief preventive strategy is the early mobilization of patients in the ICU.[21] Other measures include the use of sedation

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algorithm, resultant reduction of sedation in ICU,[22] and involvement of multidisciplinary teams for caring the critically ill. Technology as of now has reached levels where it is able to mobilize patients in ICU even when ventilated mechanically[23] or during extracorporeal membrane oxygenation therapy.[24]

The common features of ICUAW include weakness most notable in proximal neuromuscular areas.[21] Respiratory muscle involvement prolongs mechanical ventilation.[25] It is difficult to clinically classify the type of ICUAW. Critical illness myopathy is more common than critical illness polyneuropathy, and myopathy has a better rate of recovery.[26]

Aims and Objectives

In our study, the objectives were to study the incidence of ICUAW, the clinical course of weakness in the ICU, and its correlation with the duration of ICU stay.

Materials and Methods

This study was conducted in a mixed medical–surgical adult ICU of a 1,000-bedded hospital in north India. This ICU has approximately 800 to 1,000 admissions per year.

Study Design: Prospective observational study

Study Period: Fifteen months (November 1, 2015, to January 31, 2017)

Inclusion Criteria

- Patient more than 18 years of age and
- Admitted to the ICU for at least 48 hours, with
- Stable hemodynamic parameters [blood pressure maintained on ≤1 vasoactive agent (Inj. noradrenaline ≤0.2 μg/kg/min or Inj. dopamine ≤5μg/kg/min)].

Exclusion Criteria

- Patients with a history of prior neuromuscular weakness (episodic or persistent limb weakness).
- Patients admitted with neurological and neurosurgical illnesses.
- Refusal to give consent.

Study Methodology

All adult patients completing 48 hours of ICU admission and fulfilling the inclusion and exclusion criteria were included. The patient or a first-degree relative would give informed consent for participation in the study.

Baseline data collected on enrolment included age, gender, and APACHE II score at ICU admission, diagnosis, and any prior or current therapy with corticosteroids. A note was made of any aminoglycoside or neuromuscular blocker during the present hospital admission.

It is a standard protocol in the ICU to hold all sedation infusions every morning, in order to assess the awakening to patients. When the sedation score (Richmond Agitation Sedation Score) was found to be within −1 to +1, the patients underwent a baseline neurological examination by the investigator. This included assessment of consciousness by Glasgow Coma Scale, assessment of the sensory system (pin prick), deep tendon reflexes (biceps, knee, and ankle), and plantar reflexes. Note was also made of any electrolyte (sodium, potassium, chloride, calcium, and magnesium) imbalances.

We used Medical Research Council (MRC) scoring for muscle strength to assess the patients included. Six groups of muscles were tested bilaterally, including

- Shoulder abduction
- Elbow flexion
- Wrist dorsiflexion
- Hip flexion
- Knee extension
- Ankle dorsiflexion

A score of 0 was assigned for no muscle movement and 5 for normal muscle strength. When a muscle group could not be assessed that muscle group was not considered for the total score. A diagnosis of ICUAW was made if the weakness developed after ICU admission, and the average MRC score is <4 in all testable muscle groups. A neurological consultation was then sought for the same.

All included patients were followed up, and the MRC scoring was performed on alternate days during their ICU stay to study the progression of the weakness.

The outcome parameters noted were the number of days of mechanical ventilation (if intubated), duration of ICU stay, and ICU survival.

Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± standard deviation (SD) and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then a nonparametric test was used.

Statistical tests were applied as follows:

- Quantitative variables were compared using the unpaired *t*-test and Mann–Whitney Test (when the data sets were not normally distributed) between the two groups.
- Qualitative variables were correlated using the Chi-square test and Fisher's exact test.

A *p* value of <0.05 was considered statistically significant.

The data were entered in the MS EXCEL spreadsheet, and analysis was done using the Statistical Package for Social Sciences (SPSS) version 21.0.

Results and Analysis

Age

The patients studied had a mean age of 48.01 ± SD 18.06 years. The largest number of patients belonged to the 21–30 and 61–70 age-groups (53, 21.2%). Six (2.40%) patients were below 20 years, 44 (17.60%) patients were 31–40 years, 28 (11.20%) patients were 41–50 years, 42 (16.80%) patients were 51–60 years, 20 (8.0%) patients were 71–80 years, and 4 (1.60%) patients were above 80 years (Fig. 1).

Patients who developed ICUAW had a mean age of 62.64 ± 14.4 years whereas that of patients without weakness was 46.17 ± 17.65 years. Patients who developed ICUAW had a mean age significantly higher than those who did not develop ICUAW (*p* value <0.0001). The *p* value is highly significant (Fig. 2).

The frequency of developing neuromuscular weakness in the ICU showed a general trend of increase with increasing age. The *p* value for the association of age as a risk factor for developing ICUAW was found to be 0.0005, which is highly statistically significant.

Out of the 250 patients studied, 154 (61.6%) were men and 96 (38.4%) were women.

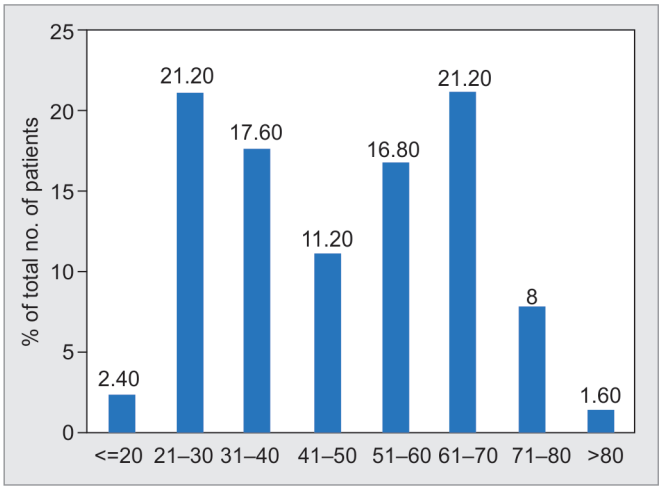

Fig. 1: Age distribution pattern of patients included in the study

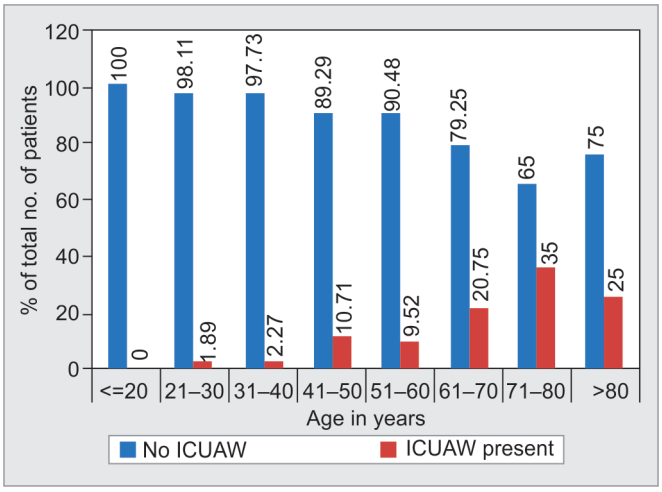

Fig. 2: Age-wise distribution of ICUAW

APACHE II Score

The patients included in our study were found to have a mean APACHE II score of 15.77 ± 5.36. There were 49 (19.60%) patients who had a score less than 10, 155 (62.0%) patients with scores 11–20, 44 (17.60%) patients with scores ranging between 21 and 30, and 2 (0.80%) patients with a score above 30 (Fig. 3) (Table 1).

Average Medical Research Council Score

The MRC score in patients who developed ICUAW showed a gradual rise from a baseline of 3.5 ± 0.41 on day 0, reaching the highest value on day 8 when it was 4.58. Thereafter on day 10, the average MRC score showed a decrease and came down to 4.04 ± 0.30, which was still higher than the day 0 value. These patients could not be followed up as according to our study protocol the follow-up was only till ICU discharge (Fig. 4).

Number of Days of ICU Stay

The 250 patients in the study were found to have 4.4 ± 2.75 days mean duration of ICU stay, with the median value of ICU stay

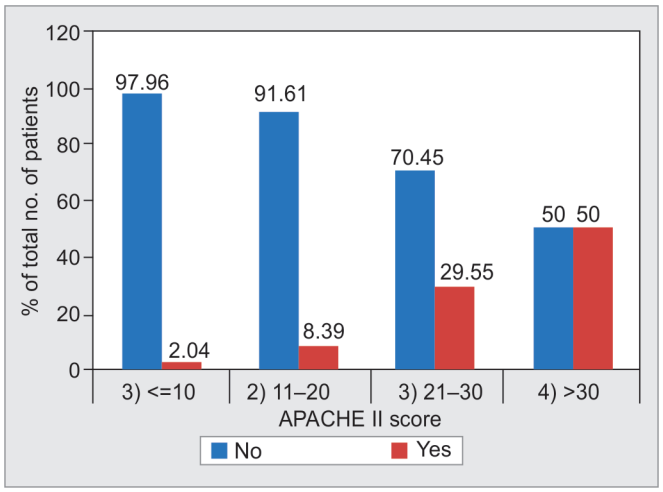

Fig. 3: Correlation of APACHE II score with ICUAW

Table 1: APACHE II score distribution

APACHE II score	*Frequency*	*Percentage (%)*
1) ≤10	49	19.60
2) 11–20	155	62.0
3) 21–30	44	17.60
4) >30	2	0.80
Total	250	100.00

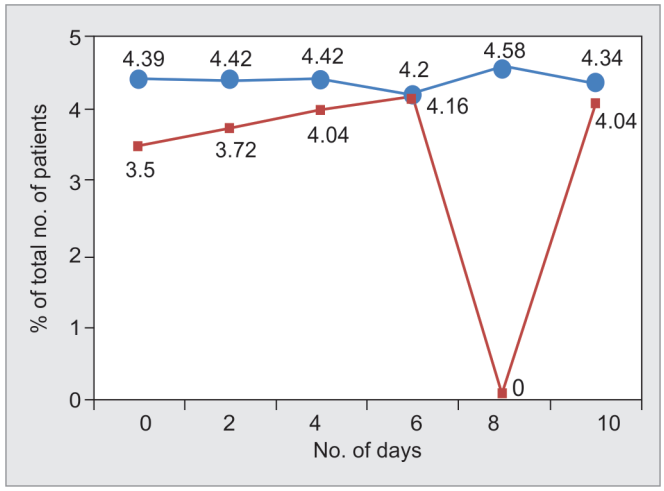

Fig. 4: Mean MRC scores in patients with and without ICUAW (*Red line—Patients with ICUAW; Blue line—Patients without ICUAW*)

duration as 4 days. The mean duration of ICU stay for patients with ICUAW was 10.93 ± 6.56 days, which was significantly higher (*p* value <0.0001) than patients who did not develop ICU stay was 5.03 ± 3.58 days (Fig. 5).

Number of Days of Mechanical Ventilation

The average number of days of intubation for the population under study was 4.35 ± 4.1 days, with a median value of 3 days. The mean duration of mechanical ventilation for patients who developed ICUAW was 9.27 ± 5.28 days, and the difference was found to be significant (*p* value <0.001). The mean duration of

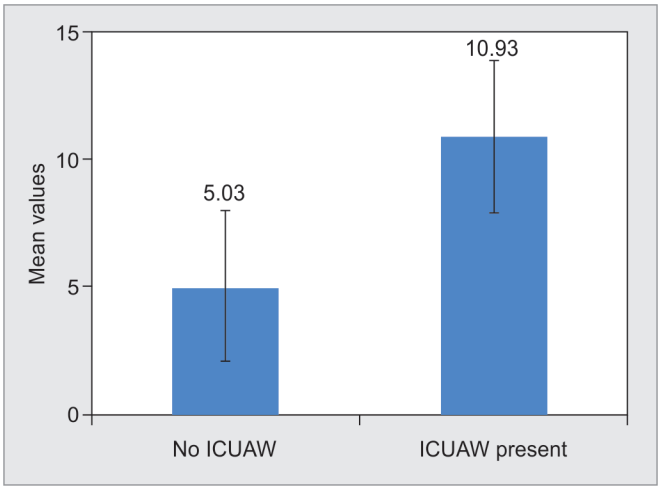

Fig. 5: Comparison of the number of days of ICU stay in patients with and without ICUAW

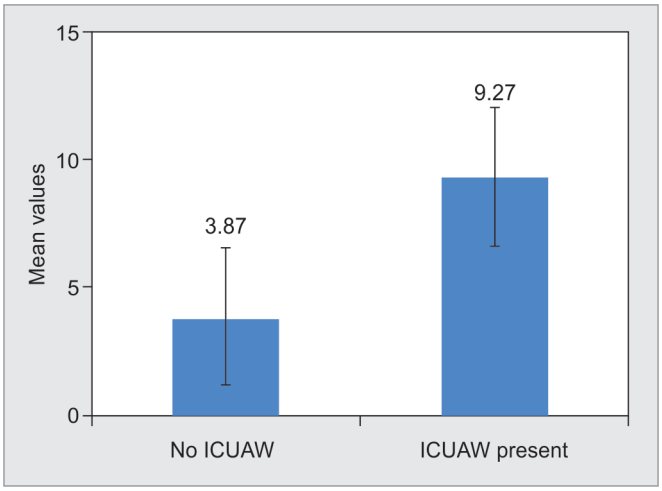

Fig. 6: Comparison of the number of days of mechanical ventilation in patients with and without ICUAW

mechanical ventilation for patients who did not develop ICUAW was 3.87 ± 3.65 days (Fig. 6).

Outcome from ICU

The number of patients who expired in the ICU was 20 (8.0%) out of the total 250 patients included. Ten (50%) out of the 20 patients who expired in ICU were documented to have ICU-acquired neuromuscular weakness. Among the 230 patients who came out alive from ICU, 18 (7.83%) developed neuromuscular weakness in the ICU. ICUAW patients had higher ICU mortality as compared to patients who did not have ICUAW (*p* value <0.0001) (Fig. 7).

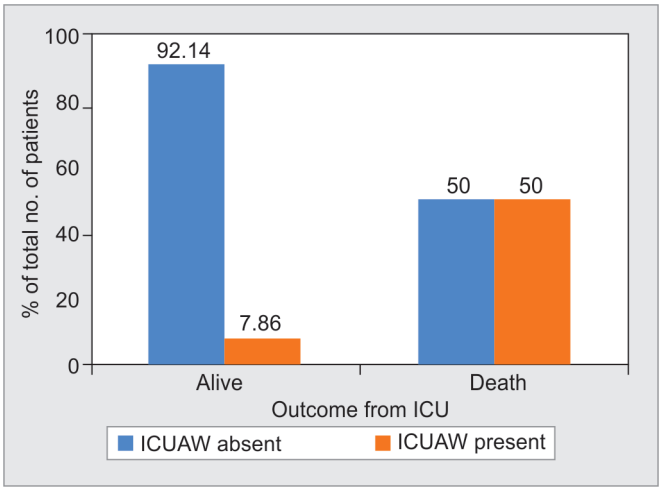

Fig. 7: Mortality and recovery among ICU patients with ICUAW

Discussion

Age

In our study, the mean age for patients who developed ICUAW was 62.64 ± 14.4 years as against 46.17 ± 17.65 years for those who did not develop the neuromuscular weakness (Figs 1 and 2), which meant the difference was statistically significant (*p* <0.0001). Bercker et al.[14] and de Jonghe et al.[7] also found a significant correlation between age and ICUAW. Patel et al.[13] noticed this independent correlation between age and ICUAW when they studied the effect of early mobilization on ICUAW. This may, to some extent, reflect the relevance of the premorbid physiological muscle reserve. The actual premorbid functional status is determined by many other factors. ICU admissions, mostly being unplanned, make it difficult to accurately document the premorbid functional status.[27] The decreasing reserve function of every organ system with advancing age is a proven fact. At the same time, it is worth mentioning that not every study on ICUAW has revealed age as an independent risk factor for developing ICUAW.

Gender

Some of the earlier studies done on ICUAW have documented female gender as a risk factor for developing ICUAW. In our study, we could not find a significant correlation between gender and ICUAW. Though there was an apparent difference with 15.63% of critically ill male patients and 8.44% female patients with critical illness developed ICUAW, this was not found to be statistically significant (*p* = 0.80). Lefaucheur et al.[10] in their prospective cohort study did not find such a correlation between gender and the incidence of ICUAW. De Jonghe et al.[7] have mentioned gender as a significant factor in ICUAW in their multicenter prospective study. As most of the studies have used Manual Muscle Testing (MMT) and MRC score average as the method of diagnosing ICUAW in both genders mostly the same values of muscle power have been applied for both genders. This may not be a correct method as the muscle mass and power before the critical illness is on average less in the female sex than that in males.[28] A cutoff force value (males, <11 kg-force; females, <7 kg-force) was found to be adequate as per Ali et al.[15] who used handgrip strength as a measure to evaluate ICU-acquired paresis. Considering these observations, it makes sense to apply gender-specific values for assessing muscle strength for the diagnosis of ICUAW. Despite this, there is no gender-specific method to assess muscle weakness till date.

APACHE Score

The mean APACHE II score on ICU admission of patients who developed neuromuscular weakness was 20.39 ± 5.22 against 15.19 ± 5.10 in patients without ICUAW, which was found to be statistically significant (Fig. 3). Most of the studies done on ICUAW have found the severity of critical illness a significant factor in the

development of ICUAW. APACHE score and Sequential Organ Failure Assessment (SOFA) score have been the commonly used parameters in assessing the severity of critical illness. Ali et al.[29] evaluated ICU-acquired paresis in critically patients by assessing handgrip strength and mortality, in a multicenter prospective cohort study and concluded APACHE score was a significant indicator of upcoming ICU-acquired paresis. This finding was also validated by Nanas et al.[18] as well as Campellone et al.[30] who investigated factors predisposing to muscle weakness caused by critical illness.

Average Medical Research Council Score

The average MRC score obtained with manual muscle testing of six sets of muscles not only helps in the diagnosis but also is used to monitor the course of the ICU-acquired neuromuscular weakness (Fig. 4). It is a simple noninvasive and cheap method, which can be performed on any cooperative patient. Various studies done globally have also shown a good interobserver agreement using MRC scoring. Ali et al.[29] found a strong correlation ($p = 0.001$) between mortality and relative reduction in ICU-free days when ICU-acquired paresis was diagnosed using MRC scoring. The significant association between mortality and reduced MRC score on the first day of awakening in ICU was resonated in the study by Sharshar et al.[31] In their study, the hospital mortality was not higher among patients who had ICU-acquired paresis persisting on day 7 when compared to patients who had recovered from ICU-acquired paresis (MRC >48/60). The major limitation of this method of evaluation is its inability to be used in unconscious and/or noncooperative patients. The limitations of the MRC scale include poor discrimination and a potential ceiling effect.[21]

Number of Days of ICU Stay

Another outcome of our study was the statistically significant increase in the number of days of ICU stay. The average durations of ICU stay were 5.03 and 10.93 days in patients with and without ICUAW, respectively (Fig. 5). The increased ICU stay comes with all its associated risks, like higher chances of nosocomial infections, ICU delirium, and many others. Not to forget the extra financial burden associated and the loss of DALYs, which fall upon the family and collectively on the nation. In a clinical review by Hermans and Van den Berghe,[27] they observed that the association between ICUAW and poor outcomes could very well be a causal one. Using MRC scoring, in a multicenter prospective study, Ali et al.[29] concluded there was a significant association between ICU-acquired paresis and ICU-free days. There can very well be a question about the role of ICUAW, as to whether it is a mere marker or it actually causes poor outcomes from ICU. This was also addressed in another study done by Hermans et al.[32] by matching weak patients to nonweak patients, and it revealed a causative relationship between ICUAW and poor outcomes from ICU.

Number of Days of Mechanical Ventilation

Patients who developed ICUAW were observed to have three times the average duration of mechanical ventilation as that of patients who did not develop ICUAW (Fig. 6). This contrast in the average length of mechanical ventilation could be attributed to the weakness of respiratory muscles, caused by the critical illness. Hermans[27] states that in a matched population of critically ill patients, the time taken for successful weaning from mechanical ventilation was significantly longer in patients who had ICUAW. At the same time, the increased duration of mechanical ventilation also increased the incidence of ICUAW.[33] In critically ill patients, an ultrasound evaluation revealed a reduction in the muscle mass during critical illness. This justifies the fact that patients with higher premorbid muscle mass stood a lesser chance of developing ICUAW. It is a standard practice to allow spontaneous breaths and thus facilitating the early mobilization of diaphragmatic muscles to minimize respiratory muscle weakness.[34,35]

Outcome from ICU

When compared to those who did not develop the weakness, ICU mortality was higher in patients who were found to have ICUAW (Fig. 7). In their prospective multicenter study published in 2008, Ali et al.[29] concluded there was an independent association between ICU-acquired paresis and increased hospital mortality. Sharshar et al.[31] found ICU-acquired paresis at the time of awakening in the ICU was associated with significantly higher hospital mortality, after adjustment for Simplified Acute Physiology Score (SAPS-II). Appleton and Kinsella[36] confirmed the devastating impact of ICUAW on the patient when they stated approximately 45% of patients diagnosed with ICUAW would die during their hospital admission. Garnacho et al.[37] did evaluate hospital mortality in a multivariable model and identified critical illness-induced neuromuscular weakness as an independent predictor of hospital mortality.

The limitations of this study are that we did not include patients below 18 years of age and our assessment of ICUAW was confined to patients with a sensorium that was good enough to be cooperative for the evaluation of muscle power. The assessment could be better with the use of more advanced technologies, like muscle ultrasound, biopsies, and electrophysiological evaluations.

Conclusion

Our study found age, APACHE score, length of ICU stay, duration of mechanical ventilation, and ICU mortality to be significantly associated with ICUAW. The difference between the average MRC scores of patients with and without ICUAW turned out significant.

ICU-acquired neuromuscular weakness (Fig. 8) remains an under-acknowledged entity despite the recent increase in awareness among caregivers. It is an important determinant of morbidity and mortality in the critically ill. Preventive strategies should be in place in all ICUs so as to ensure better prognosis

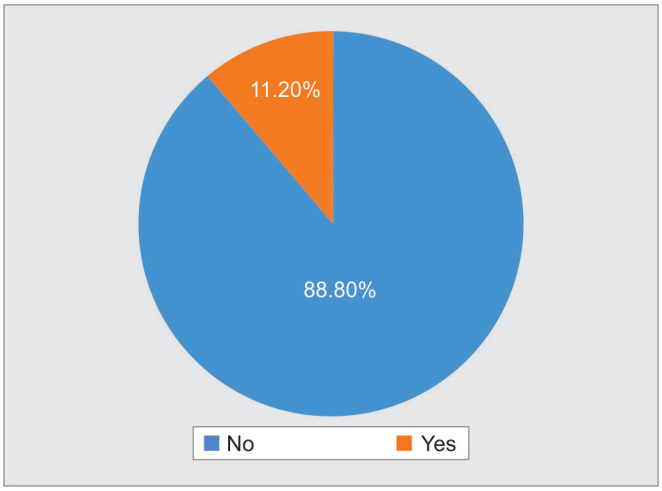

Fig. 8: Percentage of patients with ICUAW

and avoiding wastage of resources. The formulation of practice guidelines with regard to diagnosis and management can improve the current scenario. But this goal can only be achieved after thorough studies on the topics involved.

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