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RESEARCH ARTICLE

THE CORRELATION BETWEEN GRAM NEGATIVE INFECTION AND ICU – ACQUIRED WEAKNESS IN CRITICALLY ILL PATIENTS. A STUDY FROM GREECE

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Abstract

Background: ICU-acquired weakness (ICU-AW) is a clinical syndrome that occurs in critically ill patients. Weaning from the ventilator becomes difficult due to the generalized muscle weakness. The effects of ICU-AW directly affect the quality of life of patients with significant motor and sensory disabilities. This study aimed to investigate how gram-negative infections affected muscle power in patients on critical illness.

Method and Material: The study involved 99 critically ill patients in a Greek General Hospital's intensive care unit who required mechanical ventilation for over 72 hours. 21 of them had gram-positive blood cultures, identified using the "Emrora" database. The severity scales used were APACHE II, SOFA, and SAPS III. Clinical examinations of muscular strength were performed within 48 hours of ICU release, using the MRC muscle strength scale.

Results: The total MRC score of patients (21) with gram (-) microbiemia was 47.5 ± 13.5 (mean ± SD) while in the patients (19) with gram (+) it was 50 ± 14 (mean ± SD) with p=0.5. Of the 21 patients who were gram positive (-) blood culture, 7 were diagnosed with ICU-AW and had a total MRC score of 34 ±14.

Conclusions: Gram-negative microbiemia negatively impacts ICU-AW patients' muscle strength, increasing survival rates, raising concerns about long-term issues in the ICU, particularly ICU-AW. Further research is needed to understand the processes associated with SIRS and ICU-AW development.

Key words: Muscle syndrome, critical care, ICU-acquired weakness, ICU patients, gram-negative bacteremia.

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INTRODUCTION

Each year, an estimated 13-20 million people worldwide receive medical care in intensive care units (ICUs), and the occurrence of ICU-acquired weakness (ICU-AW) ranges from 25 to 31%. Factors such as age, gender, pre-existing medical conditions, and the type of administered treatment determine the annual influx of new patients, which varies between 3.25 and 6.2 million. While this progress resulted in a higher survival rate for the patients, it also revealed that they still encountered particular complications even after recovering from the illness that initially kept them in the intensive care unit.[1,2]

Currently, the scientific community is focusing on studying the immediate and long-term consequences of muscle weakness in the intensive care unit (ICU-AW). When patients experience severe motor and sensory impairments after hospital discharge, this condition directly impacts their functionality and overall quality of life. Reduced ability to perform routine activities, social isolation due to home confinement, and decreased work capability all lead to changes in mental well-being.[3]

According to clinical criteria for diagnosis, approximately 25% of severely ill patients have ICU-acquired weakness. A study conducted by Nanas et al. analyzed 185 patients who had a high APACHE II score (18.9 ± 6.6) and were hospitalized in the multi-unit intensive care unit (ICU) for more than 10 days. The study revealed that 23.8% of these individuals developed ICU-AW.[4] De Jonghe et al.[5] reported that they diagnosed ICU-AW in 25% of patients who underwent mechanical ventilation for a duration exceeding seven days. The reliance on clinical criteria for diagnosing ICU-AW, which requires active patient engagement, has hindered the ability to investigate a substantial portion of patients. Studies have shown that patients with sepsis and multiple organ failure can experience even higher incidence rates, ranging from 68% to 82%.[6,7] The study's objective was to investigate whether the presence of gram-negative microbiome affects muscle strength and contributes to the occurrence of ICU-AW.

METHODOLOGY

Study design

The hospital's Scientific Ethics Committee approved the study (215/16-07), and ensured confidentiality throughout the entire data collection and processing process, and after written informed consent, data from 86 consecutive patients admitted to ICU. In addition, any data on the participants was removed before statistical analysis was performed. Participants in the study have been properly informed about the purpose and content of the study before consenting to their participation. No data was exposed to others apart from researchers and only for the study purposes. The data were strictly confidential, and only the research team had access to them for research purposes. The two multifunctional university ICUs of a Greek hospital sequentially discharged the severely ill patients included in this observational clinical trial. These patients had been on mechanical ventilation for more than 72 hours.

Data collection

Patient history and all medical and nursing data were obtained from the medical records. Upon the patient's admission to the Intensive Care Unit (ICU), we assessed their severity scores using the Acute Physiology and Chronic Health Evaluation (APACHE II), Sequential Organ Failure Assessment (SOFA) Score, and Simplified Acute Physiology Score III (SAPS 3). Additionally, we evaluated the duration of mechanical ventilation, the length of the ICU stay, and the administration of medications. Within 48 hours of their release from the intensive care unit (ICU), scientists conducted a clinical assessment of muscle strength using the Medical Research Council (MRC) Scale for Muscle Strength and permission has been obtained for its utilization. We conducted a search in the "Emrora" database of the ICUs, specifically focusing on patients with gram-negative infections.

Inclusion criteria

Patients who met the inclusion criteria had to have been on mechanical ventilation for a minimum of 72 hours, possessed a sufficient level of consciousness, and were cooperative during the muscle strength assessment.

Exclusion criteria

Patients were precluded from the study if they were expectant, under the age of 18, or older than 85 years old, with a body mass index (BMI) greater than 35 kg/m2. Additionally, participants were ineligible if they suffered from a catastrophic fracture affecting the lower extremities, vertebrae, or pelvis, had a pre-existing neuromuscular disease, or had received a diagnosis of end-stage disease. Written informed consent was obtained preoperatively from all eligible patients or their proxies. Patients (1) who refused consent, (2) who were unable to give consent, (3) whose consent could not be obtained for logistical/emergency reasons (4)pregnant women, were also excluded.

Statistical analysis

Quantitative variables were expressed as mean (standard deviation (SD)) or median (interquartile range (IQR)). Qualitative variables were expressed as absolute and relative frequencies. The statistical analysis was conducted using the SPSS v20 software application. The determination of the level of significance was based on the p-value of each control being less than 0.05. The descriptive statistics were utilized to analyze the descriptive data. Specifically, the mean values and standard deviations (mean ± standard deviation) were computed for the demographic characteristics of the study population. The Independent T test was used to test the effect of gram (-) and gram (+) microbiota on muscle strength.

RESULTS

During the eight-month period, n=637 patients spent in the ICU between November and June from previous year, n=38 of them were removed, and n=13 more patients had no positive blood cultures. The study patients included n=86 patients, n=21 with gram-positive (-) blood culture, n=19 with gram-positive blood culture (+), n=15 with both gram(-) and gram(+), and n=31 with negative blood culture (figure 1).

The average age of the patients was 54 years (SD = 15.3 years), with n=56 (65.1%) being female and n=30 (34.9%) being female. Length of stay in the ICU were almost 22 days (SD= 17.6), where the duration of mechanical ventilation were 16 days (SD=19.3). The SOFA score was 8, with a mortality rate between 15 - 20%. The baseline characteristics of the patients are listed in Table 1 (Table 1).

Muscle strength of the patients was evaluated subsequent to their discharge from the intensive care unit, utilizing the MRC muscular strength scale (49 ± 13). It was discovered that the muscle strength of the patients had diminished considerably (MRC max = 60).Table 2 presents the MRC values for each muscle group in the upper and lower extremities of patients weighing 21 gram (-) and 19 gram (+) (Table 2).The correlation was not significant relative to the standard alpha level of .05 among muscle groups as p- value> 0.05. That indicates that each part of MRC muscular strength scale cannot lead only by itself to a correlation between microbiemia and ICU -acquired weakness in critically ill patients (Table 2).

The total MRC score of the patients (21) with gram (-) microbiota was 47.5 ± 13.5 (mean ± SD) while in the patients (19) with gram (+) it was 50 ± 14 (mean ± SD) with p< 0.1 (Table 3). While the correlation was not significantly relative to the standard alpha level of 0.05, the p-value was less than 0.10. This result remains, nevertheless, important as patients with a nosocomial infection with gram (-) or gram (+) microbiemia, stay longer in ICU and that fact affects their muscle strength (Table 3).

Among of the 55 patients whose blood cultures developed positive results, n=17 (31.5%) individuals were diagnosed with ICU-acquired infections. Among the 31 patients who had negative blood cultures, n= 11(35.5%) of them were diagnosed with ICU-aw (mean ± SD: 35.5 ± 7).

Out of the 21 patients who had a gram-positive blood culture, 7 were found to have ICU-acquired weakness (ICU-aw) and their overall MRC score was 34 ± 14 (mean ± standard deviation).

Out of the 19 patients who had a positive gramme (+) blood culture, six were diagnosed with ICU-aw. These patients had a total MRC score of 32 ± 15, which represents the mean value plus or minus the standard deviation.

Among the 15 patients who had positive blood cultures for both gram-negative and gram-positive bacteria, only 4 were identified with ICU-acquired infections. These patients had a total MRC score of 34 ± 14 (mean ± standard deviation) as shown in Figure 2 (Figure 2).

MRC muscle strength is assessed in 12 muscle groups and a summed score below 48/60 designates ICU-AW or significant weakness, and an MRC score below 36/48 indicates severe weakness. So from the above results, only the MRC muscle strength could not be a prognostic factor for ICU-AW syndrome. But in any case, muscle weakness acquired during the ICU stay is a clinically relevant complication as patients with nosocomial infection may prolong the duration of ICU stay or days in mechanical ventilation. ICU-AW should be related with many factors and not only with gram (-) microbiemia.

DISCUSSION

The current study investigated the influence of gram-negative bacteria on critically ill patients' muscular strength and the occurrence of ICU-acquired weakness (ICU-AW). The MRC muscle strength scale was used to assess the patients' muscular strength. A total of 86 patients (n = 86) were assessed, with 56 being male and 30 being female. The study revealed a substantial decline in the muscular strength of the patients (MRC = 49 ± 13).

Researchers made the intriguing discovery that patients with gram-negative microbiota had a lower overall MRC score than those with gram-positive microbiota. Furthermore, the study demonstrated that individuals infected with gram-negative bacteria exhibited inferior muscle strength in comparison to those without infection. Hermans et al. conducted research that showed an association between the occurrence of ICU-acquired weakness (ICU-AW) in patients in the intensive care unit (ICU) and the prevalence of microbiemia. They did not differentiate between gram-positive and gram-negative bacteria, and only a bivariate study demonstrated this correlation.[8]

Our study's findings did not show a statistically significant correlation between the incidence of ICU-acquired infections and the presence of gram-negative bacteria. This outcome deviates from prior investigations. The present investigation's constrained sample size could potentially explain this. An alternative explanation could be that we assessed the patients after their release from the Intensive Care Unit (ICU) instead of immediately upon their awakening. As a result, the prolonged ICU stay may have had an impact on the findings of the present study. However, the study confirmed the result of other studies that identified gram-negative bacteremia might be an independent risk factor for the development of ICU-AW.[4]

De Letter et al.'s investigation on 98 patients similarly identified SIRS syndrome as an autonomous predisposing factor for the development of ICU-AW.[9] In a study involving ninety-five patients, De Jonghe et al. identified multiple organ failure as an independent risk factor for the development of ICU-acquired weakness.[5] Subsequent effects appear independent of hemodynamic changes and are associated with pathophysiological processes involving septic mediators such as prostaglandins, cytokines, and nitric oxide. In a recent study by Nanas et al., it was formulated that Gram-bacteremia is an independent risk factor for the development of ICU-AW.[4]

The Medical Research Council score (MRC) is widely used for evaluating and diagnosing ICU-AW, but it has limitations due to patient cooperation. Recent studies suggest using ultrasound and twitch force evaluation after magnetic nerve stimulation for uncooperative patients. Electromyography (EMG) can reduce subjective errors and differentiate between CIP and CIM diagnoses, but it is not routinely used due to its time-consuming and costly nature.[10,11,12,13]

Furthermore, a subset of patients who had a more severe condition at admission (with an APACHE II score greater than 18) were analyzed to see if they had an infection caused by gram-negative bacteria. A correlation was found between the presence of gram-negative bacteria and higher APACHE II scores in patients. Hence, it is impossible to ascertain which aspect influenced this result: the gravity of the ailment or the gram-negative microbiota. Multiple studies have shown a clear relationship between the APACHE II score and the occurrence of ICU-AW, as evidenced by research conducted in the range of 13 to 17 studies. De Letter et al. discovered that the APACHE II score is a distinct risk factor for the incidence of ICU-acquired weakness.[9]

The MRC score has been found to strongly correlate with mortality and reduced ICU-free days in patients with ICU-acquired paresis. This association was also observed in a study by Sharshar et al., who found no higher mortality rates in patients with persistent ICU-acquired paresis on day 7 compared to those who had recovered. However, the MRC scale has limitations, including its inability to be used in unconscious or uncooperative patients, poor discrimination, and potential ceiling effect.[14,15] Appleton and Kinsella confirmed the devastating impact of ICUAW, with approximately 45% of patients dying during hospital admission.[16,17]

In the current study, patients were mechanically ventilated for an average of 16 ± 15.9 days, which increased their likelihood of developing ICU-acquired weakness (ICU-AW). Hermans et al. conducted research with 403 patients who had been on mechanical ventilation for more than seven days. They found that electrophysiological anomalies were present in these patients, with a potential occurrence rate of up to 50%.[18] In their study of n=139 patients with severe sepsis or septic shock who were under mechanical ventilation for more than seven days, Garnacho-Montero et al. found that patients with ICU-AW had significantly longer durations of mechanical ventilation and ventilator weaning compared to the control group.[6]

In a recent systematic review of 33 studies with a total of 2,686 patients, two main findings were reported. First, the incidence of ICU-AW after clinical diagnosis was significantly lower (32%, 95% CI: 30-35% [confidence interval]) than when the diagnosis was made by electrophysiological testing (47%, 95% CI: 45-50%), and second, the incidence of ICU-AW was estimated at 40% in patients on mechanical ventilation >7 days.[18]

The study was limited mainly by being carried out in a single center. External validation would be required to ensure its generalizability. Therefore, further studies with appropriate design are needed for future research to explore the risk factors for ICU-AW and how this syndrome is affected by nosocomial infections.

CONCLUSIONS

The study explores the impact of gram-negative bacteria on the physical strength of critically ill patients, revealing that these bacteria can increase their susceptibility to ICU-acquired weakness, a common outcome of ICU stays. This weakness, often linked to increased mortality, is often caused by prolonged mechanical ventilation. The study suggests a need for further research in post-ICU patient rehabilitation to minimize issues and evaluate the cost-effectiveness of different rehabilitation strategies.

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ANNEX

FIGURE 1. Patient Flow

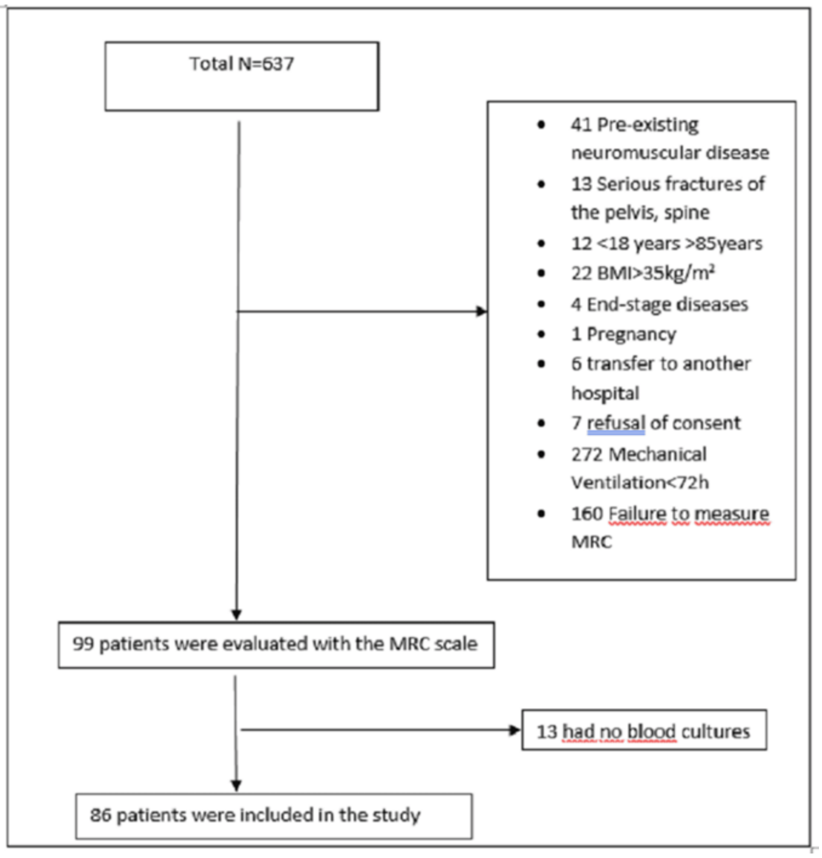

FIGURE 2. Patients with and without ICU-aw

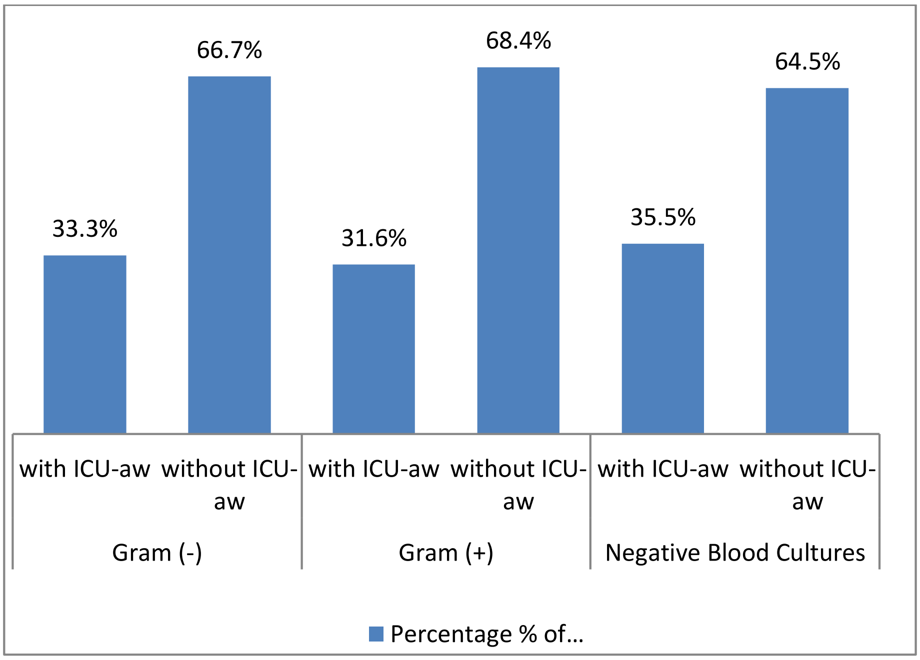

TABLE 1. Demographic Data

N=86		
Admission diagnosis:	Cardiovascular system	3
	Respiratorysystem	17
	Digestive system	14
	Neurological system	24
	Sepsis	9
	Trauma	19
Age (years)		54 ± 15.3
Weight (kg)		76 ± 14
Height (cm)		171 ± 8.9
Length of stay in the ICU (days)		22 ± 17.6
Duration of mechanical ventilation (days)		16 ± 15.9
Hospital stay after ICU (days)		21 ± 19.3
SOFA		8 ± 2.8
APACHE II		15 ± 6
SAPS III		55 ± 12.8
ICU discharge MRC value		49 ± 12.5

TABLE 2. Muscle strength as assessed by the MRC muscle strength scale

MUSCLE GROUPS	Microbiemia	Mean(SD)	P
SHOULDER BEND TO THE LEFT	gram(-)	3.5±1.2	0.63
	gram(+)	3.7±1.6	0.63
SHOULDER BEND TO THE RIGHT	gram(-)	3.6±1.2	0.34
	gram(+)	3.9±1.2	0.34
LEFT ELBOW BEND	gram(-)	4.2±1.1	0.28
	gram(+)	4.5±0.9	0.28
RIGHT ELBOW BEND	gram(-)	4.1±1.2	0.30
	gram(+)	4.5±1.1	0.30
LEFT WRIST EXTENSION	gram(-)	4.2±1	0.68
	gram(+)	4.4±1.2	0.68
RIGHT WRIST EXTENSION	gram(-)	4.2±1	0.57
	gram(+)	4.4±0.9	0.57
HIP BEND TO THE LEFT	gram(-)	3.6±1.4	0.53
	gram(+)	3.9±1.4	0.53
HIP BEND TO THE RIGHT	gram(-)	3.6±1.4	0.29
	gram(+)	4±1.3	0.29
LEFT KNEE EXTENSION	gram(-)	4±1.5	0.97
	gram(+)	4±1.5	0.96
RIGHT KNEE EXTENSION	gram(-)	4±1.5	0.81
	gram(+)	4.1±1.5	0.81
LEFT ANKLE DORSIBEND	gram(-)	4±1.4	0.59
	gram(+)	4.2±1.3	0.59
BACK BEND OF ANKLE RIGHT	gram(-)	4.2±1.2	0.72
	gram(+)	4.3±1.1	0.72

TABLE 3. Total MRC score.

	Microbiemia	Mean(SD)
ICU discharge MRC value	gram(-)	47.5 ± 13.5
	gram(+)	50 ± 14