THE RELATIONSHIP BETWEEN RISK FACTORS AND SEVERITY LEVEL OF ACQUIRED WEAKNESS ICU EVENTS IN CRITICAL PATIENTS AT DR. SOETOMO HOSPITAL

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Objectives: ICU advancements enhance critical patient survival but also raise ICU-Acquired Weakness (ICU-AW) cases due to limb weakness. ICU-AW, occurring in 47-70% of patients, lacks effective treatment, emphasizing the significance of prevention amid risk factors and patient severity considerations. Hence, this study aimed to analyze the relationship between risk factors and the severity of the incidence of ICU-AW in critical patients in the Intensive Care Unit of Dr. Soetomo Hospital, Surabaya.

Methods: This research was a cross-sectional study with 30 participants conducted in the Intensive Care Unit of Dr. Soetomo Hospital, Surabaya. SPSS was used for statistical analysis.

Results: Sepsis and SOFA Score had a significant relationship with the incidence of ICU-AW ($p<0.05$), while corticosteroid use, hyperglycemia, duration of NMBA use and sedation, and APACHE II Score did not have a significant relationship ($p>0.05$). The influence of risk factors and severity on the incidence of ICU-AW had an R2 value of 0.349, with the largest Exp(β) being sepsis. Delta (Δ) SOFA Score on day 1 and SOFA Score on day 3 had a simultaneous effect on the Nagelkerke R Square value of 0.1 and sig.0.205. SOFA Score on day 1 had an effect of 16.8%, while APACHE Score on day 1 was 1.6%.

Conclusion: In terms of risk factors and severity, sepsis and SOFA Score have a significant relationship with the incidence of ICU-Acquired Weakness.

Keywords: Serum S100β Protein Levels, Glutamate, Severity Level, Traumatic Brain Injury

Citation: Septian, D., Semedi, B. P., Susanto, K. H., Airlangga, P. S., Perdhana, F., Hamzah, & Arfianti, L. The Relationship Between Risk Factors and Severity Level of Acquired Weakness ICU Events in Critical Patients at Dr. Soetomo Hospital. Pak Heart J. 2023; x(x).

INTRODUCTION

Advances in medicine, especially in cardio-pulmonary monitoring and support for critical patients, have led to increased survival rates in intensive care units (ICUs). However, this progress has also resulted in a rise in limb weakness among ICU patients, especially those who have surpassed the critical period. Various factors, such as critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or a combination of both (CIPNM), can cause this weakness (Thabet Mahmoud et al., 2018). Determining the cause of this weakness typically requires neuromuscular tests and muscle biopsies, which are challenging to perform routinely in clinical practice (Wang et al., 2020). Therefore, the term ICU-acquired weakness (ICU-AW) is used to describe this disorder. The diagnosis of ICU-AW can be established using the Medical Research Council Score (MRC), which measures the muscle strength of the upper and lower limbs. If the score is less than 48 out of the maximum score of 60, the diagnosis of ICU-AW is made (Fontela et al., 2021).

Risk factors for ICU-AW include modifiable factors such as the use of certain medications and prolonged immobilization, as well as non-modifiable factors such as age, gender, and the severity of the underlying disease (Yang et al., 2018). ICU-AW can occur in a significant number of ICU patients, particularly those requiring prolonged mechanical ventilation (Fierro & Panitch, 2019). Although there is no effective treatment for ICU-AW, prevention through controlling risk factors, such as reducing immobilization, is a crucial step. As the number of ICU patients continues to grow, it is essential for

clinicians to understand and manage ICU-AW to enhance the quality of patient care.
The objective of this research is to analyze the relationship between risk factors and severity of the incidence of ICU-AW in critical patients in the Intensive Care Unit of Dr. Soetomo Hospital.

METHODS

This research was an observational analytical study with a cross-sectional design. The research subjects included patients undergoing treatment at the Intensive Care Unit of Dr. Soetomo Hospital, Surabaya, with a total of 30 samples. Research sampling was conducted using consecutive sampling. Inclusion criteria comprised patients treated in the ICU for more than 48 hours, those who had undergone invasive sedation and mechanical ventilation, and individuals who had been off or tapering down sedation and relaxants for more than 24 hours. Samples were excluded if they had neuromuscular disease, stroke, brain injury, spinal cord injury, peripheral vascular issues (arterial lower limb, deep vein thrombosis), motor paralysis before entering the ICU, bone fractures with internal or external fixation, cognitive impairment, and patients critically ill in the ICU who were discharged or died within 48 hours after entering the intensive care unit.

The variables examined in this study included risk factors (hyperglycemia status, sepsis, use of glucocorticoids, use of NMBA therapy, and sedation) and the severity of the incidence of ICU-AW. Data analysis was performed using SPSS to determine the significance level of each variable. The data were described using crosstabs for each variable. Then, a comparison test was conducted to ascertain the relationship between the independent variables and protective factors against the dependent variable. Nominal data were analyzed using the Chi-Square statistical test, and ordinal data were analyzed using the Mann-Whitney and Kruskall-Wallis statistical tests.

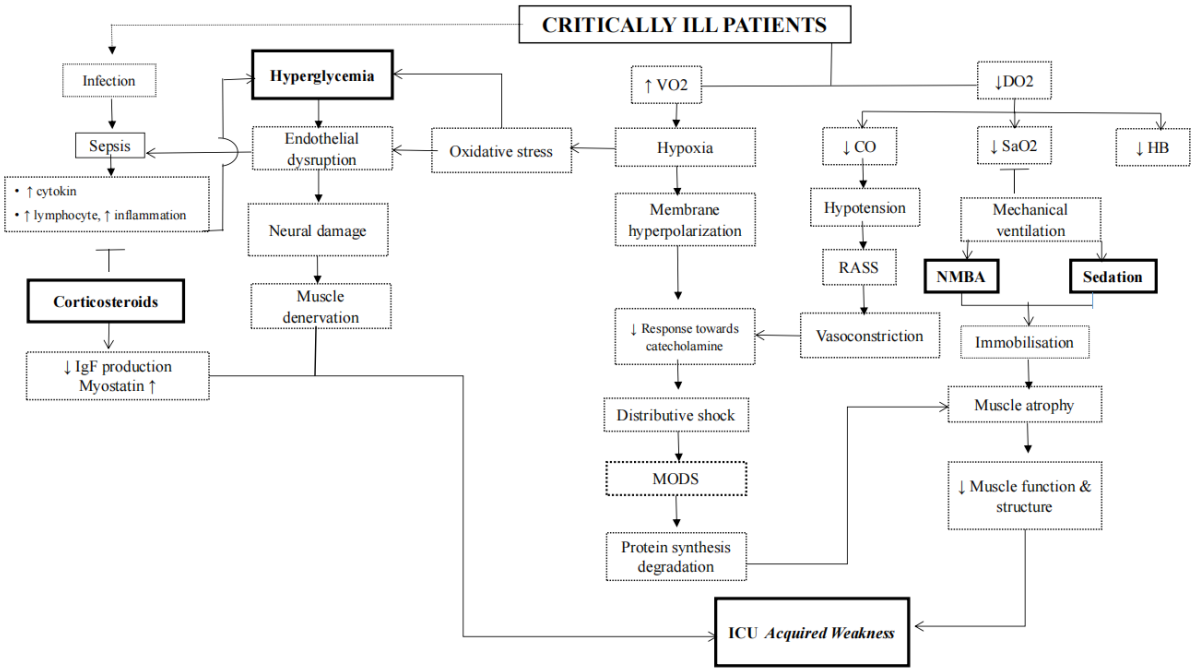

Figure (1) Research model

RESULTS

This research was carried out for 1 month, namely in the period July - August 2023, in the Intensive Care Unit of Dr. Soetomo Hospital Surabaya. Based on gender, the sample was 12 men (40%) and 18 women (60%). Based on age, the average age of the sample was 43.27 ± 14.94. Meanwhile the average BMI of the sample was 24.99 ± 8.70. Based on risk factors, it was found that 17 people (56.67%) used glucocorticoids and 13 people (43.33%) did not use glucocorticoids. Regarding the risk factors for hyperglycemia, it was found that 4 (13.33%) people experienced hyperglycemia and 26 (86.67%) people did not experience hyperglycemia. For the duration of NMBA use, the average was found to be 190 minutes (± 529.69). The duration of sedation use was

found to be an average of 1,158 minutes (± 1091.73). Meanwhile, for sepsis, it was found that only 1 (3.33%) person had sepsis, and 29 (96.67%) people did not experience sepsis. Based on the severity level, the SOFA Score found that 1 (3.33%) person had a SOFA Score in the range 0-1 and 29 (96.67%) people had a SOFA Score ≧2. In the APACHE II Score, it was found that 4 people (13.33%) had an APACHE II Score in the range 0-4, 0 people had an APACHE II Score in the range 5-9, 4 people (13.33%) had an APACHE II Score in the range 10-14, 8 people (26.67%) had APACHE II Score in the range 15-19, 9 people (30%) had APACHE II Score in the range 20-24, 3 people (10%) had APACHE II Score in range 25-29, 2 people (6.67%) had an APACHE II Score in the range 30-34, and 0 people had an APACHE II Score ≧35. Based on the incidence of ICU AW, it was found that 24 people (80%) experienced ICU AW events based on the MRC score.

Table (1) Sample Characteristics

Gender	ICU AW		p Value
	Yes (%)	No (%)	
Male	9 (75)	3 (25)	0,09[a]
Female	15 (83)	3 (17)	
totally	24 (80)	6 (20)	

Age	ICU AW		p Value
	Yes (%)	No (%)	
6-19	0 (0)	1 (100)	0,14[b]
20-29	4 (80)	1 (20)	
30-39	7 (87.5)	1 (12.5)	
40-49	6 (86)	1 (14)	
50-59	3 (100)	0 (0)	
≥ 60	4 (67)	2 (33)	
Totally	24 (80)	6 (20)	

BMI	ICU AW		p Value
	Yes (%)	No (%)	
<18,5	1 (100)	0 (0)	0,07[b]
18,5-22,9	10 (91)	1 (9)	
23-24,9	10 (77)	3 (23)	
25-29,9	0 (0)	0 (0)	
≥ 30	3 (60)	2 (40)	
Totally	24 (80)	6 (20)	

a= chi square test, b= T test independent

Table (2) Relationship between Risk Factors and Severity Levels with Incidence of ICU Acquired Weakness

Risk Factors	p value
Glucocorticoid use	1.000
Hyperglycemia	0.557
Duration of NMBA use	0.571
Duration of sedation use	0.053
Sepsis	0.042
SOFA Score	0.042
APACHE II Score	0.831

As shown in table 2, Sepsis and SOFA Score have a significant relationship with the incidence of ICU Acquired Weakness ($p<0.05$). Glucocorticoid use, hyperglycemia, duration of NMBA use, presence or absence of NMBA use, duration of sedation use, presence or absence of sedation use, and APACHE II Score did not have a relationship with the incidence of ICU Acquired Weakness ($p>0.05$).

Table (3) Logistic regression analysis of risk factors and severity on the incidence of ICU Acquired Weakness

	β	Sig.	Exp (β)	CI 95%	R^2
Corticosteroid use	-0.314	0.748	0.730	0.77–6.898	0.349
Hyperglycemia	18.851	0.999	154	0.000	
Duration of NMBA use	0.000	0.986	1.000	0.996-1.004	
Duration of sedation use	-0.001	0.228	0.999	0.997-1.001	
Sepsis	22.446	1.000	559	0.000-1.000	
APACHE II Score	0.151	0.715	1.163	0.517-2.617	
SOFA Score day 1	22.446	1.000	559	0.000-1.000	

The results in Table 3 showed that the combined influence of the independent variables (risk factors and severity) on the dependent variable (ICU-AW incidence) was 34.9%, with the remaining influenced by other variables. Meanwhile, based on the significance value (sig), it can be concluded that none of the independent variables has a partial effect on the incidence of ICU-AW (sig. > 0.05).

Table (4) Comparison of severity levels between SOFA Score on day 1 and APACHE II Score on day 1 of the incidence of ICU Acquired Weakness

	Omnibus test	Nagelkerke R Square	Sig.
SOFA day 1	0,67	0,168	1,000
APACHE II day 1	0,576	0,016	0,574

From table 4, it is evident that the SOFA Score on day 1 has a more significant impact on the incidence of ICU-AW, accounting for 16.8%, whereas the APACHE II Score on day 1 has an effect of 1.6%.

Discussion

This study aims to analyze the relationship between risk factors and the severity of the incidence of ICU-AW in critical patients in the Intensive Care Unit of Regional General Hospital Dr. Soetomo Surabaya.

The use of corticosteroids was not associated with the incidence of ICU-AW. This aligns with research conducted by (Yang et al., 2018), which concluded that the effect of corticosteroids on the occurrence of ICU-AW is still controversial. Hyperglycemia (GDA > 200 mg/dl) has no association with the incidence of ICU-AW, differing from (De Jonghe et al., 2009). A large body of evidence supports hyperglycemia as a risk factor for ICU-AW, identified over 15 years ago in an observational study of a small population of ICU patients (Callahan & Supinski, 2009).

The duration of NMBA use and the presence or absence of NMBA use were not associated with the incidence of ICU-AW. This contradicts the results of research by (Yang et al., 2018), which stated that in the five studies analyzed, NMBA and the incidence of ICU-AW had a significant relationship. However, those studies focused on NMBA use, not the duration of use. The duration of NMBA use in the ICU may indeed be associated with the incidence of ICU-AW, and it is essential to note that long-term use of NMBAs is considered a risk factor for ICU-AW.

The duration of sedation use and the presence or absence of sedation use were not related to the incidence of ICU-AW. The duration of sedation in the ICU can be a complex factor to consider in relation to the incidence of ICU-acquired weakness (ICU-AW). Although prolonged sedation can cause muscle weakness, it is crucial to understand that the relationship is not determined solely by the duration of sedation. ICU-AW is a multifactorial condition influenced by various factors, including immobility, systemic inflammation, critical illness neuropathy, myopathy, and many more. Although sedation can cause immobility and disabling muscle atrophy, this is only one of many potential causes of ICU-AW.

Sepsis has a significant relationship with the incidence of ICU-AW. This aligns with research by Yang et al. (2018), which stated that SIRS (OR, 3.75; 95% CI, 1.59-8.86) and duration of SIRS in the first week (days) > 3 (RR 3.74; 95% CI, 1.37-10.2) were considered significant risk factors for the development of ICU-AW based on multivariate analysis. Sepsis (OR, 2.20; 95% CI, 1.30-3.71) and days with sepsis (HR, 1.48; 95% CI, 1.22-1.81) were also found to be statistically significant with ICU-AW (Witt et al., 1991). Sepsis and ICU-acquired weakness are related in several ways, as sepsis is one of the main causes of ICU-acquired weakness. Sepsis is a life-threatening condition caused by the body's extreme response to infection, triggering a systemic inflammatory response known as a “cytokine storm,” which can cause widespread inflammation throughout the body, affecting various organs and tissues, including muscles (Purcarea & Sovaila, 2020).

The SOFA Score has a significant relationship with the incidence of ICU-AW. This is consistent with research conducted by (Li et al., 2021). The SOFA score is indirectly associated with acquired frailty in the ICU by various mechanisms. It provides a measure of the overall severity of a patient's critical illness. Patients with higher SOFA scores often experience more severe organ dysfunction and critical illness, increasing the risk of complications such as ICU-AW. Patients with more severe organ dysfunction, as reflected by SOFA scores, may require a longer ICU stay. Prolonged immobilization and bed rest, common in the ICU, are known risk factors for ICU-AW (Lambden et al., 2019). Higher SOFA scores may be associated with a greater risk of infection, especially in patients with compromised immune function. Infection can cause systemic inflammation, which may play a role in the development of ICU-AW (Liu et al., 2022).

There was no relationship between APACHE II Score and the incidence of ICU-AW. Compared with the SOFA Score on day 1, the APACHE II Score on day 1 only had a 1.6% effect on the incidence of ICU-AW, while the SOFA Score on day 1 had an effect of 16.8%. These results differ from research by Yang et al. (2018), which stated that the five studies analyzed had a significant relationship with the incidence of ICU-AW. However, in that study, the inclusion criteria for APACHE II were >12, while in this study, there was no minimum APACHE II score. So, the final results of the research could be different. APACHE II focuses on physiological parameters relevant to predicting short-term mortality, such as vital signs, oxygenation, and laboratory values. This assessment does not include specific assessments of muscle strength or function, important in the diagnosis of ICU-AW. The APACHE II score can help identify patients at higher risk of complications and death in the ICU. Although a higher APACHE II score may indicate more severe disease, it does not directly predict the development of ICU-AW. ICU-AW risk assessment usually involves evaluating specific factors such as the duration of sedation, immobility, and the use of neuromuscular blocking agents, in addition to other clinical assessments (Zhou et al., 2022).

CONCLUSION

Based on the results and discussions presented, the following conclusions can be drawn: In terms of risk factors, only sepsis has a significant relationship with the incidence of ICU-Acquired Weakness. Meanwhile, the use of corticosteroids, hyperglycemia, duration of NMBA use, presence or absence of NMBA use, duration of sedation use, and presence or absence of sedation use had no relationship with the incidence of ICU-Acquired Weakness. At the severity level, the SOFA Score has

a significant relationship with the incidence of ICU-Acquired Weakness. Meanwhile, the APACHE-II Score has no relationship with the incidence of ICU-Acquired Weakness. The influence of risk factors and severity on the incidence of ICU-Acquired Weakness was only 34.9%, with the highest influence being sepsis. The SOFA Score on day 1 is more influential when compared to the APACHE Score on day 1.

This research has limitations. In this study, we did not control the patient's length of time in the ICU, which could be a confounding variable and thus influence the research results. Additionally, patient comorbidity data has not been considered in this study. However, this research is the first in Indonesia to discuss the incidence of ICU-AW.

AUTHORS' CONTRIBUTION

DS & BPS,: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to beaccountable for all aspects of the work. BPS, PSA & KHS, PSA, FP, H, and LA: Data acquisition, interpretation, drafting, final approval and agree to be accountable forall aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

REFERENCES

1. Callahan, L. A., & Supinski, G. S. (2009). Hyperglycemia and acquired weakness in critically ill patients: potential mechanisms. In *Critical care (London, England)* (Vol. 13, Issue 2). https://doi.org/10.1186/cc7728
2. De Jonghe, B., Lacherade, J. C., Sharshar, T., & Outin, H. (2009). Intensive care unit-acquired weakness: Risk factors and prevention. *Critical Care Medicine*, *37*(SUPPL. 10). https://doi.org/10.1097/CCM.0b013e3181b6e64c
3. Fierro, J. L., & Panitch, H. B. (2019). Transitioning from an ICU ventilator to a portable home ventilator. *Seminars in Fetal and Neonatal Medicine*, *24*(5). https://doi.org/10.1016/j.siny.2019.101041
4. Fontela, P. C., Glaeser, S. S., Martins, L. F. G., Condessa, R. L., Prediger, D. T., Forgiarini, S. G. I., Forgiarini, L. A., Lisboa, T. C., & Friedman, G. (2021). Medical research council scale predicts spontaneous breathing trial failure and difficult or prolonged weaning of critically ill individuals. *Respiratory Care*, *66*(5). https://doi.org/10.4187/RESPCARE.07739
5. Lambden, S., Laterre, P. F., Levy, M. M., & Francois, B. (2019). The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Critical Care*, *23*(1), 1–9. https://doi.org/https://doi.org/10.1186/s13054- 019-2663-7
6. Li, M., Shao, H., Wang, C., Chen, C., Ye, L., Ding, M., Ren, S., Zhao, X., Wang, X., & Qin, B. (2021). Risk factors and their predictive value for intensive care unit acquired weakness in patients with sepsis. *Chinese Critical Care Medicine*, *33*(6). https://doi.org/10.3760/cma.j.cn121430-20210329-00459
7. Liu, C., Suo, S., Luo, L., Chen, X., Ling, C., & Cao, S. (2022). SOFA Score in relation to Sepsis: Clinical Implications in Diagnosis, Treatment, and Prognostic Assessment. *Computational and Mathematical Methods in Medicine*, *2022*. https://doi.org/10.1155/2022/7870434
8. Prabhakar, H. (2017). *Essentials of neuroanesthesia*. Academic Press.
9. Purcarea, A., & Sovaila, S. (2020). Sepsis, a 2020 review for the internist. *Romanian Journal of Internal Medicine = Revue Roumaine de Medecine Interne*, *58*(3). https://doi.org/10.2478/rjim-2020-0012
10. Thabet Mahmoud, A., Tawfik, M. A. M., Abd el naby, S. A., Abo El Fotoh, W. M. M., Saleh, N. Y., & Abd El Hady, N. M. S. (2018). Neurophysiological study of critical illness polyneuropathy and myopathy in mechanically ventilated children; additional aspects in paediatric critical illness comorbidities. *European Journal of Neurology*, *25*(7). https://doi.org/10.1111/ene.13649
11. Wang, W., Xu, C., Ma, X., Zhang, X., & Xie, P. (2020). Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. In *Frontiers in Medicine* (Vol. 7). https://doi.org/10.3389/fmed.2020.559789
12. Witt, N. J., Zochodne, D. W., Bolton, C. F., Grand'Maison, F., Wells, G., Young, G. B., & Sibbald, W. J. (1991). Peripheral nerve function in sepsis and multiple organ failure. *Chest*, *99*(1). https://doi.org/10.1378/chest.99.1.176
13. Yang, T., Li, Z., Jiang, L., Wang, Y., & Xi, X. (2018). Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. In *Acta Neurologica Scandinavica* (Vol. 138, Issue 2). https://doi.org/10.1111/ane.12964
14. Zhou, J., Zhang, C., Zhou, J. D., & Zhang, C. K. (2022). Effect of early progressive mobilization on intensive care unit-acquired weakness in mechanically ventilated patients: An observational study. *Medicine (United States)*, *101*(44). https://doi.org/10.1097/MD.0000000000031528

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