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Risk factors of Intensive Care Unit-Acquired Weakness: a single center retrospective analysis

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Abstract: ICU acquired muscle weakness (ICU-AW) is a central feature of protracted critically ill patients. Severity of critical illness, interventions, such as the administration of neuromuscular blocking agents and aminoglycosides, and markers in the blood, such as hyperglycemia, have been associated with ICU-AW. Prediction models for ICU-AW have been disappointing. This retrospective analysis aimed to investigate known risk factors of ICU-AW in a single center 36 bed ICU of a non-university teaching hospital.

ICU-AW was diagnosed by the MRC-SUM test in awake patients (score <48). Risk factors, derived from the literature, were classified in three classes (patient characteristics, ICU interventions and laboratory variables). Only values, known within the first two days of ICU stay were taken into account. The most relevant factors concerning ICU-AW were selected by comparing patients with and without ICU-AW, stratified by the three classes.

Patient characteristics were most discriminative between patients with and without ICU-AW. Only the need for endotracheal intubation for at least 2 days was a relevant intervention associated with ICU-AW. None of the laboratory variables differed between patients with and without ICU-AW. Female gender ($p<0.001$), unplanned admission ($p=0.007$), suspected sepsis ($p=0.006$), and severity of acute critical illness (APACHE IV score) on admission ($p<0.001$) were different in patients with ICU-AW. In the multivariate logistic regression model female gender (odds ratio 2.50, 95%CI 1.63-3.84, $p<0.001$), APACHE IV score (odds ratio 1.01, 95%CI 1.01-1.02, $p=0.029$) and need for endotracheal intubation for at least 2 days (odds ratio 2.14, 95%CI 1.31-3.48, $p=0.002$) remained independent risk factors of ICU-AW. However, their discriminative power for ICU-AW had only an AUROC of 0.681 (95%CI 0.631-0.730) ($p<0.001$).

Patient characteristics on admission appeared to differ most in patients with ICU-AW, in compared to patients without. Female gender, severity of critical illness and prolonged need of intubation are strongly associated with ICU-AW.

Keywords: Critical illness; muscle weakness; polyneuropathies; sepsis.

Introduction

Intensive Care Unit-acquired weakness (ICU-AW) has been recognized as an important and persistent complication in survivors of critical illness. Its incidence is approximately 50% in the severely ill ICU population. Moreover, ICU-AW is associated with longer mechanical ventilation, a prolonged stay in the ICU and in the hospital, and an increased mortality (1, 2).

While ICU-AW has a protracted course, it develops early after ICU admission, depending on the severity of the acute critical illness and the ensuing organ failure. This muscle weakness can emerge from either critical illness polyneuropathy (CIP), from critical illness myopathy (CIM) or from both (1, 3-7).

It is well known that syndromes such as sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) are thought to play an important role in the development and pathophysiology of ICU-AW. The study of various risk factors, such as the need or use of vasopressors, corticosteroids, neuromuscular blocking agents (NMBAs), parenteral nutrition or aminoglycosides,

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the occurrence of hyperglycemia or the duration of endotracheal intubation (ETT) has suggested that early prediction of ICU-AW could be important for prevention of ICU-AW and to detect the patients, benefitting most from early mobilization in the ICU (3, 8-10).

In 2014 Wieske et al. (11) were the first to develop an early prediction model for ICU-AW. In this prospective study of 212 patients, who were mechanically ventilated for ≥ 2 days, their prediction model included 3 easily available factors, i.e. highest lactate, treatment with any aminoglycoside and age. They also discovered an improvement in discrimination, comparing the new prediction model to the maximal SOFA score and APACHE IV score in the first two ICU days. Discriminative performance of this model seemed reasonable with an AUROC of 0.71 but in a multicenter external validation study of 349 patients this performance could not be reproduced (12). Hence, a new model with the same 3 factors (lactate, aminoglycoside and age), derived from a cohort of 536 patients, was developed with only a fair AUC-ROC of 0.70 [95% CI: 0.66-0.75], comparable with that of the original model.

In 2018, a more extensive predictive model for ICU-AW was developed in multicenter cohort of 4157 patients, who were ventilated for ≥ 12 hours. This model used 6 variables (steroid therapy, intensive insulin therapy, sepsis during mechanical ventilation, acute renal failure, hematologic failure, days on mechanical ventilation). It had good discrimination (AUC-ROC: 0.81 [95% CI: 0.78-0.84]), but is was scored on the first day that the patient was awake (13). Besides, the incidence of ICU-AW was only 3%, probably due to under-diagnosing of ICU-AW, which was diagnosed by a vague definition of flaccid paresis during two consecutive days. No standardized technique such as electromyography or MRC-SUM scoring was used.

In a meta-analysis of 14 studies on ICU-AW it was found that only the severity of acute critical illness (Acute Physiology and Chronic Health Evaluation II score) and the use of neuromuscular blocking agents or aminoglycosides were consistently associated with ICU-AW (14).

Most authors therefore concluded that currently no reliable model for the early prediction of ICU-AW exists. This single center retrospective study thus aimed to gain insight into the factors associated with ICU-AW in the mixed medical/surgical ICU population in the ICU of Ziekenhuis Oost-Limburg, Genk, Belgium. As validation of existing prediction models is premature, the primary goal was to create early awareness of possibilities to prevent muscle weakness and its consequences. The secondary goal of this study was to create a new predictive model of Intensive Care Unit-acquired weakness, if possible.

Methodology

Patient population

This study was a retrospective analysis of data, collected from all patients, admitted to the 36-bed mixed medical and surgical intensive care unit of Ziekenhuis Oost-Limburg in Genk, Belgium from the 27th of September 2016 until the 17th of September 2019. The study was approved by the independent Ethics Committee of ZOL-Genk and adhered to the STROBE guidelines on retrospective analyses.

Diagnosis of ICU-AW: the Medical Research Council Sum score (MRC-SUM)

At the beginning of this period, the MRC-SUM scoring was introduced to detect ICU-AW in the framework of the early mobilization program of prolonged critically ill patients. There were no strict in- or exclusion criteria for the patients to be assessed. At the discretion of the physiotherapists, MRC-SUM measurements were done in patients who were either expected to, or were staying longer in the ICU.

The MRC-SUM test is a volitional functional assessment of the peripheral muscles. It consists of the bilateral scoring of shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and ankle dorsiflexion. Each of the 6 muscle groups is scored according to 6 categories, ranging from 0 (no contraction) to 5 (normal muscle force). The maximum score is 60. ICU-AW is conventionally defined as an MRC-SUM <48 and severe weakness at MRC-SUM <36. The most important shortcoming is that patients need to be awake and cooperative in order to perform the MRC-SUM test.

Patient characteristics

From all patients who underwent an MRC-SUM test during their ICU stay demographics (age and sex) were collected together with following on-admission variables i.e.: (un)planned admission, suspected sepsis or presence of shock at time of admission, the systematic use of corticosteroids prior to ICU and the APACHE IV score.

Variables in ICU treatment

With the help of an automated search of patient files by CTCue software (CTcue B.V. Amsterdam, The Netherlands) on the electronic health records of the patients, admitted to the ICU during the study period, it was possible to retrieve eleven binary variables. Only values within the first 2 days were taken into account, since we aimed to look at variables for the early prediction of ICU-AW. Following variables in early ICU treatment were analyzed: endotracheal intubation for 2 or more days and the use of following ICU treatments in the first 2 days of admission: any NMBA, aminoglycosides, norepinephrine, vasopressin, phenylephrine, dobutamine, epinephrine, IV corticosteroids, insulin and the use of renal replacement therapy. Likewise, possibly important laboratory parameters during the first 2 days of ICU stay were retrieved by the CTcue software from the patients' electronic health records: min. and max. ionized calcium (mmol L^{-1}), min., max. and mean glycemia (mg dL^{-1}), max. lactate (mmol L^{-1}), min. and max. thrombocytes (10^9 L^{-1}), min. and max. pH and min. albumin (g L^{-1}). The variables were based on the laboratory values that were used in previous prediction models.

Statistical analyses

Continuous data were presented as mean ± SD or median (IQR) and compared by, respectively, Student t-test or Mann-Whitney test, as appropriate. Categorical data were presented as numbers (percentage) and compared by chi square tests.

Univariate and multivariate logistic regression analysis was done for the prediction of ICU-acquired weakness following ICU admission. In these models, variables with p-values of less than 0.1, when comparing patients with and without ICU-AW, were included. Differences were considered significant when two-sided p values were 0·05 or less. No corrections were made for multiple comparisons. All analyses were performed with JMP (version 14; SAS Institute Inc., Cary, NC).

Results

Study population

During the study period from the 27th of September 2016 until the 17th of September 2019 in 477/7597 (6.3%) patients, admitted to the ICU, at least one MRC-SUM measurement was done within the first 30 days of their ICU stay. In 466 of these patients, enough data on factors linked with ICU-AW could be collected.

Table 1

Incidence of risk factors of ICU-AW during the first two days of ICU stay

Study population of 466 patients	**N (%)**
Unplanned admission	348 (75%)
Suspected sepsis on admission	201 (43%)
Presence of shock on admission	252 (54%)
Systemic use of corticosteroids prior to ICU	25 (5%)
Endotracheal intubation ≥ 2 days	134 (29%)
Any NMBA use	230 (49%)
Aminoglycoside	67 (14%)
Noradrenaline at any dose	337 (72%)
Dobutamine at any dose	25 (5%)
Adrenaline at any dose	24 (5%)
Vasopressin at any dose	28 (6%)
Intravenous corticosteroids	186 (40%)
Intravenous insulin therapy	300 (64%)
Renal replacement therapy	43 (9%)

Abbreviations: NMBA = Neuromuscular Blocker Agent.

At least one MRC-SUM measurement was below 48 (i.e. ICU-AW) in 305/466 (65%) patients. There was a large variation in the incidence of risk factors of ICU-AW during the first two days of their ICU stay (Table 1). MRC-SUM measurements were also performed in patients not requiring endotracheal intubation for at least 2 days (n=332, 71%). The APACHE IV score was median 68 (54-83) and the mean MRC-SUM score was 44 ± 9.

Clinical characteristics of patients with and without ICU-AW

The proportion of female sex, unplanned ICU admission and suspected sepsis on admission was higher in the patients with ICU-AW (Table 2). Only the need for endotracheal intubation for at least 2 days was higher in patients with ICU-AW later on (Table 3). The severity of acute critical illness, as reflected in the APACHE IV score, was also higher in the patients with ICU-AW ($p<0.001$).

Laboratory results during the first two days in patients with and without ICU-AW

Previously described laboratory variables to predict ICU-AW did not differ between patients

Table 2

Demographics and admission characteristics

	ICU-AW (N = 305)	**No ICU-AW (N = 161)**	**P-value**
Age, years	71 (62-79)	69 (61-77)	0.102
Female	145 (48)	43 (27)	**<0.001**
Unplanned admission	240 (79)	108 (67)	**0.007**
Suspected sepsis	146 (48)	55 (34)	**0.006**
Presence of shock	173 (57)	79 (49)	0.119
Systemic use of corticosteroids prior to ICU	17 (6)	8 (5)	0.833
APACHE IV score	72 (57-84)	64 (51-77)	**<0.001**

Categorical values are presented as n (%). Continuous values are presented as median (IQR). Abbreviations: ICU = Intensive Care Unit.

Table 3

ICU treatment

	ICU-AW (N = 305)	**No ICU-AW (N = 161)**	**P-value**
Endotracheal intubation ≥ 2 days	103 (33)	31 (19)	**0.001**
Any NMBA use	150 (49)	80 (50)	0.923
Aminoglycoside use	50 (16)	17 (11)	0.097
Norepinephrine use	226 (74)	111 (70)	0.276
Vasopressin use	23 (8)	5 (3)	0.065
Phenylephrine use	29 (10)	11 (7)	0.387
Dobutamine use	18 (6)	7 (4)	0.526
Epinephrine use	16 (5)	8 (5)	1.000
IV use of corticosteroids	127 (42)	59 (37)	0.321
Insulin therapy	198 (65)	102 (63)	0.761
Renal replacement therapy	33 (11)	10 (6)	0.129

Categorical values are expressed as n (%). Abbreviations: IV = Intravenous; NMBA = Neuromuscular Blocker Agent.

with and without ICU-AW in our study population (Table 4), except for the lower minimal ionized calcium levels in patients with ICU-AW.

Univariate and multivariate models for ICU-AW

Important risk factors for ICU-AW (p-value <0.1) were entered in a univariate (left panel) and multivariate (right panel) logistic regression model for the prediction of ICU-acquired weakness following ICU admission (Table 5). Calcium levels (minimum and maximum) were omitted from the multivariate analysis due to collinearity. Eventually, only female sex, APACHE IV score and need of at least two days of endotracheal intubation remained independent risk factors for ICU-AW later on during ICU stay. A predictive model with the latter 3 variables had an area under de receiver operator characteristics curve (AUROC) of 0.681 (95% CI: 0.631-0.730) (p<0.001) (Fig. 1).

Discussion

As the first goal of this study was to analyze risk factors of ICU-AW to create early awareness in the prevention of the condition, the secondary aim was to construct a predictive model to detect the patients most at risk of ICU-AW, which could allow to take preventive measures or to dedicate the physiotherapy resources more specifically to

Table 4

Laboratory variables

	ICU-AW (N = 305)	No ICU-AW (N = 161)	P-value
Min. ionized calcium, in mmol L^{-1}	1.05 (0.94-1.12)	1.07 (0.98-3.68)	**0.004**
Max. ionized calcium, in mmol L^{-1}	1.21 (1.17-1.28)	1.23 (1.17-4.58)	0.058
Min. glycemia, in mg dL^{-1}	93 (79-104)	93 (79-105)	0.765
Max. glycemia, in mg dL^{-1}	203 (176-241)	206 (173-251)	0.712
Mean glycemia, in mg dL^{-1}	142 (128-152)	143 (130-154)	0.564
Max. lactate, in mmol dL^{-1}	2.60 (1.65-4.80)	2.40 (1.70-3.85)	0.337
Min. thrombocytes, in 10^9 L^{-1}	157 (112-208)	153 (113-214)	0.709
Max. thrombocytes, in 10^9 L^{-1}	215 (165-281)	207 (168-283)	0.872
Min. pH	7.30 (7.23-7.36)	7.30 (7.24-7.36)	0.749
Max. pH	7.47 ± 0.05	7.46 ± 0.05	0.542
Min. albumin, in g L^{-1}	28.5 ± 6.1	29.1 ± 5.94	0.327

Table 5

Univariate and multivariate logistic regression analysis for the prediction of ICU-acquired weakness following ICU admission

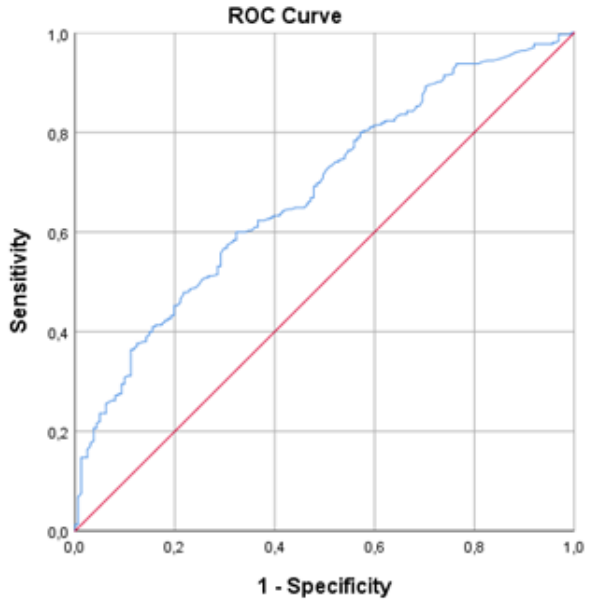
Variables	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Female sex	2.49	1.64-3.77	**<0.001**	2.50	1.63-3.84	**<0.001**
APACHE IV score	1.02	1.01-1.03	**<0.001**	1.01	1.01-1.02	**0.029**
Suspected sepsis	1.77	1.19-2.63	**0.005**	1.53	1.00-2.34	0.051
Unplanned admission	1.81	1.18-2.78	**0.006**	-	-	-
ETT ≥ 2 days	2.14	1.35-3.38	**0.001**	2.14	1.31-3.48	**0.002**
Aminoglycoside use	1.66	0.92-2.99	0.090	-	-	-
Vasopressin use	2.54	0.95-6.83	0.064		-	-
Min. ionized calcium	0.72	0.62-0.84	**<0.001**	-	-	-
Max. ionized calcium	0.80	0.70-0.91	**<0.001**		-	-

Note: min. ionized and max. ionized calcium were removed from multivariate logistic regression analysis due to collinearity. Unplanned admission was omitted as well since it is included in the APACHE IV score. Abbreviations: ETT = Endotracheal Intubation.

the weakest patients. However, the variables taken from ICU-AW prognostic models barely differed in patients with ICU-AW, compared to patients without. Only female gender, severity of critical illness (APACHE IV) and prolonged need of endotracheal intubation were strongly associated with ICU-AW.

The fact that we could not demonstrate an association between classical risk factors of ICU-AW, such as neuromuscular blocking agents and aminoglycosides, and ICU-AW, measured by a functional test, may be linked to a shift in clinical practice. Long term administration of the latter drugs was common practice in early days of critical care. Nowadays, sedation with and without neuromuscular blocking agents and antibiotic administration are kept as limited as possible to avoid complications such as ICU-AW and antibiotic resistance. In our study 49% received at least one single dose of any NMBA. This differed to the now less common practice of continuous infusions or multiple doses of NMBA's.

Laboratory variables differentiated poorly patients with and without ICU-AW. Understandably, single lab values are not representative for patients. Therefore, the APACHE IV score incorporates 11



AUROC = 0.681 (0.631 – 0.730): p<0.001

Fig. 1. - ROC curve of predictive model with variables female sex, APACHE IV score and need of at least two days of endotracheal intubation

laboratory values, creating collinearity with e.g. the lab variables pH and albumin. Hyperglycemia, requiring intensive insulin therapy, has been associated with polyneuropathy and eventually ICU-AW. As a large proportion of prolonged critically ill patients receive intensive insulin therapy as part of the ICU protocol, the relationship between hyperglycemia and ICU-AW may be less apparent in this population.

Female gender as a risk factor for ICU-AW is somewhat surprising as it has been consistently shown that women have better survival from critical illness compared to males, even when matched for severity of illness and comorbidities. Whether this may be related to the lower baseline muscle strength (i.e. population norm values that are age corrected) compared to males is unknown. Gender may be added to the APACHE IV score as it does not include gender, despite being an important independent predictor of survival from critical illness.

In a recent meta-analysis, only the Acute Physiology and Chronic Health Evaluation II score was associated with ICU-AW across several studies, together with neuromuscular blocking agents and aminoglycosides. The APACHE IV score is an updated version of the APACHE II and takes into account the ICU admission diagnosis by adding a coefficient. Both scores can reasonably predict hospital mortality and ICU length of stay.

This study has several limitations. First, it is a single center study in which some risk factors may be less present. Second, ICU-AW was only diagnosed through the MRC-SUM measurements. This is only possible in awake patients and may have led to a bias by excluding sedated patients. ICU-AW can be diagnosed by electromyography only in the latter patients. Third, the lack of a protocol on the inclusion criteria to start the MRC-SUM measurements may have induced a bias as well. The MRC-SUM may have been done in the most cooperative patients as it may be more reliable in these patients. Also the timing of the MRC-SUM measurements was not standardized. Hence, the measurements may have been done at different phases of critical illness.

From our study it can be concluded that it is too early for reliable prediction models of ICU-AW. Patients with high APACHE scores and requiring endotracheal intubation for at least 2 days may be the best population to start systematically measuring MRC-SUM scores in.

Author contributions

CH: Participated in the design of the study and analysis plan, performed the database searches, checked the database for accuracy, drafted the manuscript.

DS: Performed the patient assessments

BN: Performed the patient assessments

MVL: Supervised patient recruitment, revised the manuscript for important intellectual content.

WB: Supervised patient recruitment, revised the manuscript for important intellectual content.

KE: Supervised patient recruitment, revised the manuscript for important intellectual content.

TF: Supervised patient recruitment, revised the manuscript for important intellectual content.

XW: Supervised patient recruitment, revised the manuscript for important intellectual content.

NP: Set-up of database and help with database searches

SR: Revised the manuscript for important intellectual content.

WE: Participated in the design of the study, performed the statistical analyses, revised the manuscript for important intellectual content.

DM: Supervised study design and analysis plan, drafted the manuscript.

References

1. van Wagenberg L, Witteveen E, Wieske L, Horn J. Causes of Mortality in ICU-Acquired Weakness. J Intensive Care Med. 2017:885066617745818.
2. Kramer CL. Intensive Care Unit-Acquired Weakness. Neurol Clin. 2017;35(4):723-36.

3. Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015;19:274.
4. Batt J, Herridge M, Dos Santos C. Mechanism of ICU-acquired weakness: skeletal muscle loss in critical illness. Intensive Care Med. 2017;43(12):1844-6.
5. Jolley SE, Bunnell AE, Hough CL. ICU-Acquired Weakness. Chest. 2016;150(5):1129-40.
6. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020;46(4):637-53.
7. Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007;131(5):1541-9.
8. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev. 2014(1):Cd006832.
9. Wolfe KS, Patel BK, MacKenzie EL, Giovanni SP, Pohlman AS, Churpek MM, et al. Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients. Chest. 2018;154(4):781-7.
10. Patel BK, Pohlman AS, Hall JB, Kress JP. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. Chest. 2014;146(3):583-9.
11. Wieske L, Witteveen E, Verhamme C, Dettling-Ihnenfeldt DS, van der Schaaf M, Schultz MJ, et al. Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study. PLoS One. 2014;9(10):e111259.
12. Witteveen E, Wieske L, Sommers J, Spijkstra JJ, de Waard MC, Endeman H, et al. Early Prediction of Intensive Care Unit-Acquired Weakness: A Multicenter External Validation Study. J Intensive Care Med. 2018:885066618771001.
13. Penuelas O, Muriel A, Frutos-Vivar F, Fan E, Raymondos K, Rios F, et al. Prediction and Outcome of Intensive Care Unit-Acquired Paresis. J Intensive Care Med. 2018; 33(1):16-28.
14. Yang T, Li Z, Jiang L, Wang Y, Xi X. Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. Acta Neurol Scand. 2018;138(2):104-14.