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Is age-adjusted MEWS upon admission a relevant prognostic tool for final outcome?

Да ли коригована вредност *MEWS* скора према старости при пријему има прогностичку вредност у односу на коначан исход лечења?

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Да ли коригована вредност MEWS скора према старости при пријему има прогностичку вредност у односу на коначан исход лечења?

SUMMARY

Introduction/Objective Early warning scoring systems are important for timely identification of the critically ill, but are they a relevant prognostic tool? Our objective was to test if Modified Early Warning Score (MEWS), lactate and base excess (BE) have any prognostic value in high dependency unit (HDU) patients.

Methods This was a prospective observational study that included 364 patients who were treated at respiratory HDU. The values of MEWS, lactate and BE at admission were recorded with patients' age, sex and comorbidities. Negative outcome was defined as death or transfer to Intensive Care Unit (ICU). Independent predictors of negative outcome were identified with the use of multivariable logistic regression.

Results Of 369 patients, 203 (55%) were male. Mean age was 62 ± 16. There were 138 (37. 4%) patients with negative outcome: 27.37% died, while 10.03% patients required ICU transfer. The median length of hospital stay was 13 days [IQR 7–15]. Patients with negative outcome had a significantly higher MEWS (3.68 ± 1.965 *vs.* 4.57 ± 2.33, p < 0.001), lower BE (-0.139 ± 7.48 *vs.* -3.751 ± 6.159, p < 0.001), and a higher lactate (2.299 ± 2.350 *vs.* 3.498 ± 3.578, p < 0.001). MEWS ≥ 4 (OR 1.90, CI 1.082–3.340, p = 0.026) was the only independent predictor of mortality. Area under the curve for MEWS with regard to in-hospital mortality prediction was 0.633 (95% CI 0.569–0.697). When age was added to MEWS, the AUC was 0.76 (95% CI 0. 707–0.814).

Conclusion Our findings support the prognostic value of MEWS for final outcome of patients admitted to High Dependency Unit.

Key words: MEWS; lactate; BE; outcome.

САЖЕТАК

Увод/циљ Бодовни системи за рано препознавање су важни за идентификацију критично оболелих, али да ли су и прогностички алат? Циљ је био проверити прогностичку вредност модификованог раноупозоравајућег бодовног скора (*MEWS*), лактата и базног ексцеса (БЕ) код болесника примљених у Јединицу полуинтензивне терапије (ЈПТ).

Методе Проспективна опсервациона студија обухватила је 369 болесника хоспитализованих у пулмолошку ЈПТ. Вредности *MEWS* скора, лактата и БЕ при пријему забележене су, као и доб болесника, пол и присуство коморбидитета. Негативни исход је дефинисан као смрт или премештај у Јединицу интензивног лечења (ЈИЛ). Фактори за које је униваријантном анализом утврђена статистичка значајност анализирани уз помоћ мултиваријантне логистичке регресије, у циљу утврђивања независних предиктора неповољног исхода.

Резултати Од укупно 369 болесника, 203 (55%) су били мушкарци, а просечна старост је била 62 ± 16 година. Неповољан исход лечења забележен је код 138 (37,41%) болесника: 27,37% је умрло; а 10,03% болесника премештено је у ЈИЛ. Просечна дужина хоспитализације била је 13 дана [*IQR* 7–15]. Болесници са неповољним исходом имали су значајно веће вредности *MEWS* (3,68 ± 1,965 *vs.* 4,57 ± 2,33, *p* < 0,001), нижи БЕ (-0,139 ± 7,48 *vs.* -3,751 ± 6,159, *p* < 0,001), и виши лактат (2,299 ± 2,350 *vs.* 3,498 ± 3,578, *p* < 0,001). *MEWS* ≥4 (*OR* 1,90, *CI* 1,082–3,340, *p* = 0,026) се издвојио као једини независни предиктор морталитета. Површина испод криве (*AUC*) за *MEWS* у функцији предиктора морталитета била је 0,633 (95% *CI*, 0,569–0,697). Корекцијом у односу на старост болесника, *AUC* је била 0,76 (95% *CI* 0,707–0,814).

Закључак Резултати студије потврђују прогностичку вредност *MEWS* бодовног система у односу на коначан исход лечења болесника Јединице полуинтензивног лечења.

Кључне речи: *MEWS*; лактат; БЕ; исход

INTRODUCTION

Various versions of early warning scores (EWS) are proposed for timely identification of critically-ill [1-4]. The ultimate goal is to timely recognize clinical deterioration, which facilitates early intervention. One of the wide spread scores in clinical practice is a Modified Early Warning Score (MEWS) [5-7]. In the most recent study EWS was also proposed as a prognostic tool, but further validation is necessary [8]. Addition of laboratory findings to

increase the value of clinical scores has been considered [9-22]. Since our respiratory High Dependency Unit (HDU) is mainly used for treating the patients diagnosed with pneumonia and sepsis, severe COPD exacerbation and pulmonary thromboembolism, we decided to test lactate, base excess (BE), and age in, addition to MEWS, as predictors of final outcome.

METHODS

This study was prospective and observational. It took place in the respiratory High Dependency Unit of Institute for Pulmonary Diseases. The study was done in accordance with the Committee on Ethics of the Institute for Pulmonary Diseases of Vojvodina. During the time period from 2009 until 2014, following data were recorded for 369 patients: age, sex, comorbidities, vital signs and the calculated MEWS at admission, as well as lactate and BE at admission, length of stay, and outcome. There were 501 patients treated in the respiratory HDU during the given time period; however, due to technical issues, it was not possible to measure lactatemia in 132 patients, and they were omitted from the study. Negative outcome was either Intensive Care Unit (ICU) transfer or death, and positive outcome was discharge from the hospital or transfer to the general ward. We used the following cut-off values: MEWS≥4, lactate≥2.5 mmol/1, age ≥65years and BE<-2 mmol/l. We used percentages to present categorical variables and their comparison was performed with the help of either Fisher 's exact test or chi-square. Either mean [±SD] or median [interquartile range - IQR] were used to present continuous variables and the values were further compared using student T test or Mann-Whitney U test. Odds ratio between individual factors and mortality were calculated with univariate logistic regression, followed by multivariable logistic regression in order to recognize independent mortality predictors. Sensitivity and specificity at the given cut-off of ≥4 points were determined for MEWS score, followed by the ROC (receiver-operating characteristic) curve.

RESULTS

Mean age of 369 patients was 62 (±16) years. There were 215 (58.3%) male patients. Leading diagnosis at admission was pneumonia for 151 patients (40.92%). As many as 341 (92.4%) had at least one comorbidity – mostly cardiovascular. Age, sex, co-morbidities and initial diagnosis upon admission for all patients are listed in Table 1.

No difference was found in MEWS values between the patients with and without co-morbidities (Table 2).

Initial MEWS was taken in all patients, as well as lactate, BE, and the length of stay. All the values were compared between the groups with positive and negative outcome. 231 (62.6%) patients had a positive outcome. Patients with negative outcome had a significantly higher MEWS (3.68±1.965 vs. 4.57±2.33, p<0.00l), low er BE (-0.139±7.48 vs. -3.751±6.159, p<0.001), and a higher lactate (2.299±2.350 vs. 3.498±3.578, p<0.00l).We found no difference in the length of stay between the groups with different outcome (17.00± 11.697 vs. 14.44± 18.709, p=0.106).

We correlated initial MEWS with lactatemia and found a weak positive correlation (r=0.245, p<0.001).

We also compared initial MEWS with BE and found a weak positive correlation (r=0.202, p<0.001).

Median length of hospital stay was 13 days [IQR 7-15]. We did not find that patients with MEWS≥4 had more hospital days (17.00±11.697 vs, 14.44±18.709, p=0.61). Odds ratio between individual factors and mortality were calculated with univariate logistic regression, and the identified factors that had a correlation with mortality were: MEWS≥4 points, lactate ≥2,5 mmol/l, BE<-2 mmol/l, as well as age ≥65 and presence of comorbidities (Table 3).

In the following step potential independent mortality predictors were identified with the use of multivariable logistic regression – results are shown in Table 4. Multivariate logistic regression showed that MEWS and age were independent mortality predictors. Strongest predictor of mortality was MEWS with OR of 1.9.

The area under the curve for MEWS was 0.633 (95% CI 0.57-0.70). The model which included age and MEWS (AUC 0.76, 95% CI 0.707-0. 814) was superior to MEWS alone (AUC 0.633, 95% CI 0.569- 0.697). The calculated AUC for BE was only 0.338 with 95% CI 0.272-0.404 and AUC for lactate was 0.652 with 95% CI 0.585-0.718. The addition of both lactate and BE to the model which included MEWS and age did not improve the AUC (AUC 0.79, 95% CI of 0.740-0.843).

DISCUSSION

Rationale behind the use of early warning scores is quite straightforward—their crucial clinical role lies in timely recognition of clinical deterioration on the ward. Acute deterioration is most frequently preceded by changes in vital parameters, which constitute EWS [1-10]. In this study we confirmed the predictive value of MEWS and age in identifying HDU patients at high risk for death or ICU admission. Further addition of BE and lactate were not found to improve the outcome prediction.

Alam et al presented the results of systematic review on impact of EWS on patient outcomes. Seven large studies were included but meta-analysis was not possible due to heterogeneity. They concluded that there was a positive trend towards improved outcomes after early warning scores were introduced [3] Main limitation of this review was the fact that no single standardized EWS was used. One of the best validated variants of EWS is a modified early warning score (MEWS). Implementation of this score has shown reduction in hospital mortality, number of ICU days and number of adverse events [5-7]. When our

respiratory HDU was established in April of 2009, we choose to incorporate MEWS in the chart. One of the aims was to demonstrate its effectiveness in every day practice in order to introduce it to our general wards without too much resistance from the already overburdened staff.

The study was prospective and observational in design, but is has several limitations. The first limitation is that we excluded 132 patients due to the fact that our laboratory could not perform lactate testing at all times. Second limitation is that „initial" MEWS, along with lactate and BE refers to the values measured upon admission to the respiratory HDU—more than half of the patients were transferred from the ward, while the rest were admitted directly to HDU. Another limitation is that comorbidities were noted but Charlson comorbidity index was not calculated in order to better classify their burden and severity.

We found that 341 (92.4%) patients had at least one comorbidity, but there was no difference in initial MEWS values between the groups with and without comorbidities. In the study by Cildir et al there was a significant difference between surviving patients and those who died both in MEWS values and Charlson comorbidity index, but the two indices were not compared to each other [23].

Initial MEWS values were compared between the groups with different outcome. Due to a specific role of a HDU, we defined positive outcome as either transfer to the ward or discharge from the hospital, while death and transfer to ICU were defined as a negative outcome. Total of 231 (62.6%) patients had a positive composite outcome, and patients with negative composite outcome had a significantly higher MEWS. This finding is in accordance with the results of Goldhill et al – they conducted a study on 1047 patients where they concluded that an increasing EWS was associated with higher hospital mortality [1]. Burch et all conducted a study on 790 patients and they also found that increasing MEWS was associated with higher rates of intrahospital mortality [5]. Similarly, early

warning scores were previously tested as potential predictors of serious adverse events in hospitals. Ludikhuize et al performed a study which included 204 patients. They found that 81% patients had MEWS score three points or higher on all at least one occasion during the forty-eight hour period preceding the adverse event [6].Recently Liu et all performed a cohort study in patients with and whitout the infection comparing 5 early warning score regarding their potential role to predict in-hospital mortality and the combined outcome of ICU transfer or mortality. National Early Warning Score and MEWS had the highest discrimination power to predict the outcome in comparison with the Quick Sequential Sepsis-Related Organ Failure Assessment (qSOFA), and Systemic Inflammatory Response Syndrome (SIRS) [2].

Median length of hospitalization in our study was 13 days [IQR 7-15]. We did not find that patients with initial MEWS ≥4 had a longer length of stay (LOS). Also, we found no difference in the length of hospitalization between the groups with positive and negative outcome. In a large study for MEWS validation, Subbe et al showed that 7.1% of all patients had MEWS≥5 at admission compared to only 1.8% on day three [7]. However, in the recent study by Kruisselbrink et al in a resource limited setting, median duration of hospitalization was 9 days. The authors found much higher percentages of MEWS≥5 after a median of 9 days [4]. Torsvik et al conducted a post intervention study in a Norway hospital on 409 patients, and the intervention included introduction of a flow chart for sepsis identification including all vital parameters, doctors' response time and treatment. They found that the length of stay was 3.7 days shorter after the intervention. Explanation is that timely identification of high-risk patients leads to earlier intervention and/or shorter delay to ICU transfer [24]. However, in the study by Paterson et al the results showed that LOS extended significantly in relation to increasing EWS score, and also that EWS score of ≥4 resulted in

doubling of the hospitalization length [25]. Similarly, Groarke found that higher admission EWS correlated with longer hospital stay [26].

In our study, risk factors for higher mortality in univariate analysis were: MEWS≥4 points, lactate≥2.5 mmol/l, BE <-2 mmol/I, presence of comorbidities and age of ≥65. Multivariable logistic regression analysis identified two independent mortality predictors: MEWS and age. In the study by Jacques et al BE of less than -5 mmol/1 was also confirmed as a predictor of serious adverse events [2]. Groarke et al found that admission early warning score can be valuable score for triage in acute medical admissions - they concluded that there was a higher risk for ICU admission, as well as death for, for each rise in early warning score category [26]. Paterson et al designed a study to assess effects of a standardized early warning score on patient outcomes in acute admissions – they included 848 patients, both medical and surgical. The results confirm that high admission early warning score indicated higher risk of hospital mortality. Moreover, the medical staff filled a questionnaire where they indicated the use of a scoring system helped detect illness severity (80%) which prompted earlier interventions (60%) [25]. One of the most significant early studies for MEWS validation by Subbe et al found that MEWS of ≥5 points correlated with increased risk for mortality as well as ICU admission. Kruisselbrink et al found that MEWS above four points was associated with increased mortality [7]. However, the most recent argument in favor of MEWS is the study whose results were published in 2016 by Churpek. The study compared four different scores in order to determine their value in predicting hospital mortality and transfer to Intensive care. The scores were: MEWS, quick Sequential Organ Failure Assessment score (qSOFA), National Early Warning Score (NEWS) and Systemic Inflammatory Response Syndrome (SIRS). The study included 30677 patients who first met the criteria for suspected infection from 2008 until 2016. The results show that NEWS was the best predictor of hospital mortality, and MEWS was the

second best. Authors conclude that the newly proposed qSOFA score is not a good substitute for early warning scores when it comes to identifying high-risk patients with suspected infection [8]. Another study published in 2016 by Wang et at [27] established that peri -arrest MEWS values predicted the outcome. On the other hand, Italian study published in 2017 on 526 patients with sepsis states that even though increasing MEWS correlates with mortality, AUC did not show that MEWS had a sufficient sensitivity for predicting in-hospital mortality [28]. Mitsunaga et al showed that NEWS and MEWS predict hospital mortality in the elderly. [29]

There are studies in which addition of biochemical markers increased the area under the curve for predicting intra-hospital mortality. Perera et al found that MEWS of ≥5 points predicted outcome, along with increasing age. In order to increase sensitivity of prediction, they suggested a combined score consisting of MEWS and several biochemical parameters: CRP, albumin and platelet count [30]. Ho et al showed that combining plasma lactate with quick SOFA score significantly increases the ability to predict mortality in patients with infection [11]. Our study did not demonstrate additional benefit of adding BE and lactate level to the age and MEWS in predicting mortality risk in HDU patients. It is possible that this is due to heterogeneity of the population – we included patients with pneumonia, sepsis, but also acute COPD exacerbation and pulmonary thromboembolism. Further research in each of these subgroups may show different results.

CONCLUSION

The findings of our study suggest that modified early warning score, adjusted for age, represents a valuable prognostic tool for final outcome and an independent predictor of hospital mortality for High Dependency Unit patients. According to the recent studies about the significance of early warning scores to predict outcome in hospitalized patients, results

of our study are another contribution to use them for identifying the patients at risk for inhospital death or need for transfer the patients to the intensive care units.

Conflict of interest: None declared.

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Table 1. Baseline characteristics of the patients

Variables		**N (%)**
Sex	Male	215 (58.3%)
	Female	154 (41.7%)
Comorbidities	Cardiovascular	260 (70.5%)
	Respiratory	143 (38.8%)
	Neurological	73 (19.8%)
Age	< 65	180 (48.8%)
	≥ 65	189 (51.2%)
Diagnosis at admission	Pneumonia	151 (40.92%)
	Chronic obstructive pulmonary disease	78 (21.1%)
	Sepsis	59 (16%)
	Pulmonary embolism	28 (7.6%)
	Respiratory failure in neurological diseases	8 (2.17%)

Table 2. Modified early warning score in patients with and without comorbidities

Modified early warning score							
		< 4		≥ 4		Total	
		N	%	N	%	N	%
Comorbidities	Without	13	7.5%	15	7.7%	28	7.6%
	With	160	92.5%	181	92.3%	341	92.4%
	Total	173	100%	196	100%	369	100%

Table 3. Univariate logistic regression model to estimate unadjusted odds ratios between each factor and mortality

Variables	OR	95% CI	p
Modified early warning score ≥ 4	2.119	1.296–3.465	0.003
Lactate ≥ 2,5	2.477	1.531–4.008	< 0.001
Base Excess < -2 mmol/l	2.579	1.68–4.516	< 0.001
Age ≥ 65	1.069	1.046–1.093	< 0.001
Comorbidities	4.732	1.101–20.337	0.037

Table 4. Multivariate logistic regression analysis showing independent predictors of mortality

Variables	Cut-off values	p	OR	95% CI
Modified early warning score	≥ 4	0.026	1.901	1.082–3.340
Lactate	≥ 2.5	0.173	1.479	0.842–2.591

