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FUTURE CHALLENGES: INTERVENTIONS TO MODIFY RISK FACTORS THAT INFLUENCE NEGATIVELY THE OUTCOME OF CRITICALLY ILL PATIENTS

SHPATA V.[1]*, KURTI F.[1], KREKA M.[1], ÇELA A.[1] AND OHRI I.[2]

[1]Faculty of Medical and Technical Sciences, University of Medicine in Tirana, Albania
[2]Department of Anesthesia and Intensive Care, Faculty of Medicine, University of Medicine in Tirana, University Hospital Center "Mother Theresa", Tirana, Albania
*Corresponding Author: Email- vjollca.hajro@yahoo.com

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Abstract- Mortality in intensive care unit (ICU) patients remains high. Long stays in ICU are associated with high costs and burdens on the healthcare system, especially in our country, where healthcare resources are constrained. The aim of the study: To investigate risk factors for mortality and prolonged ICU stay in critically ill patients.

Methods: The prospective cohort study was performed in the surgical and medical ICU of University Hospital Center of Tirana.

Results. The results of multiple regression analyses adjusted for confounders estimating the risk factors for complications, longer ICU stay and mortality, were age above 60 years, high APACHE II score, nosocomial infection, mechanical ventilation, malnutrition at ICU admission and cumulated energy deficit during ICU stay.

Conclusions. Modifiable risk factors for poor clinical outcome of ICU patients were nosocomial infection, malnutrition and cumulated energy deficit. Knowing the risk factors can be improved patient care. Optimizing resource planning in the early detection and treatment of infection and in the screening for malnutrition and implementing nutrition support may decrease health care costs in this population.

Keywords- intensive care unit, mortality, prolonged ICU stay, nosocomial infection, complications, malnutrition, cumulated energy deficit, critically ill

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Introduction

Mortality in intensive care unit patients remains high, it was reported to be 6.4% to 40% [1]. Prolonged ICU stay can adversely affect the health status by increasing the risk of infection, complications, and, possibly, mortality [2]. Long stays and complications in ICU are associated with high costs and burdens on the healthcare system [3,4]. The cost of caring for patients in ICUs has been estimated to account for 1-2% of the gross national product and 15-20% of hospital costs, which represents 38% of total healthcare costs in US [5]. There is a growing need to adjust clinical practice to improve the quality of care in ICU as well as conserve medical resources. The identification of modifiable risk factors for ICU mortality and poor clinical outcome is the initial step of a strategy that could lead to identification of patients at risk and special interventions that could contribute to better and more cost-effective management of our patients and reduction of ICU mortality.

Although risk factors for mortality and long stays in the ICU have been reported in the medical literature, there isn't any study about risk factors for poor prognosis in Albanian ICUs.

This study sought risk factors for mortality, complications and longer ICU stays, that have potential to be modified among patients treated in medical or surgical intensive care units. The aim of the study was to determine the independent role of each risk factor associated with ICU mortality, complications and longer ICU stay, in the hope that this information could provide a basis for the development of new policies to improve patient care and decrease the cost of ICU treatment, especially in the conditions of our country, where healthcare resources are constrained.

Materials and Methods

In this prospective cohort study, we evaluated the factors associated with ICU mortality among patients that stayed in medical/surgical ICU for more than 4 days, who were assumed to require prolonged physiologic support and were, therefore, theoretically at increased risk for nosocomial infection, complications and mortality. The study was conducted in the 15-bed medical and surgical ICU of University Hospital Center of Tirana "Mother Theresa" in Albania during January 2010-December 2013. Data were made anonymous for analysis. The study have been conducted in accordance with the princi-

ples of the Declaration of Helsinki of the World Medical Association, and was approved by the ethics committee of the Faculty of Medicine of Tirana in Albania.

Patient data

We recorded demographic variables (age and gender), admission diagnosis and type of hospital admission (emergency or elective). ICU admission diagnosis were classified as [6]: respiratory (asthma/ allergy, COPD exacerbation, non-cardiogenic pulmonary edema, respiratory arrest, respiratory infection, pulmonary embolus), cardiovascular (hypertension, rhythm disturbance, congestive heart failure, hypovolemic/cardiogenic shock, coronary artery disease, post cardiac arrest), neurologic (seizure disorders, intracranial/subdural/ subarachanoid hemorrhage), other non-operative (intoxication, diabetic ketoacidosis, gastrointestinal bleeding, other metabolic/ renal, other respiratory, other neurological, other cardiovascular, other gastrointestinal), trauma (multiple trauma, head trauma), post-operative (post-operative chronic cardiovascular disease, post-operative with hemorrhagic shock, post-operative gastrointestinal bleed, post-operative gastrointestinal neoplasm, postoperative respiratory insufficiency, post-operative gastrointestinal obstruction/ perforation). To control for the influence of severity of illness on ICU mortality and clinical outcome, we evaluated the severity of illness using the Acute Physiological and Chronic Health Evaluation (APACHE II) [7] upon admission to the ICU. Nutritional status on admission was assessed according to Nutritional Risk Screening 2002 [8]. The patients with a total score ≥ 3 was considered at nutritional risk. Undernutrition was evaluated by any of the 3 variables (BMI, recent weight loss, recent food intake).

As in our clinic is not available indirect calorimetry, energy target was set at 25 kcal/kg/day according to the ESPEN guidelines [9]. Energy delivery: total delivery includes energy from enteral and parenteral feeds, from non-nutritional sources (glucose and glucosaline infusions used for drug dilution and fluid support). Energy balance was calculated as energy delivery-energy target, on daily basis. Data were collected on the nutritional risk screening, the time of start of feeding after ICU admission, energy delivery, and cumulated energy balance at the end of ICU stay.

Clinical Follow-Up

Length of ICU stay (ICU LOS) and length of ventilator stay, total complications, ICU acquired infections and ICU mortality were recorded. Complications were defined to be the appearance of a disease condition in addition to the preexisting condition which motivated ICU admission, without a specific relationship between the two. Complications can be ICU acquired infections (infections that become evident 48 hours or more after admission in the ICU: systemic inflammatory response syndrome [10], pneumonia, urinary tract infection, central venous catheter sepsis, sepsis [11] and wound infection [12]) and other complications: post-operative (open abdominal wound, post-operative bleeding, anastomotic leak), neurological, respiratory, gastointestinal, cardiovascular, hepatic failure (by SOFA), renal failure (by SOFA) [13], and coagulation disorder. Length of ICU stay was measured in days, from the day of ICU admission to ICU to the time of discharge or ICU death.

Statistical analysis: Data are presented as the mean ± SD (standard deviation) for numerical variables, number (n) or percentage (%) for categorical variables. A multiple logistic regression was applied to examine possible independent predictors of clinical outcomes and is calculated the odds ratio (OR) and its confidence interval (CI). Categorical data were analyzed using the Ch^2 test. Statistical significance was considered at the level of $p \leq 0.05$. All tests were two tailed. SPSS 15.0 statistical package used to analyze the data.

Results

We studied 963 patients ≥ 18 years, stayed more than 4 days in the ICU of University Hospital Center of Tirana "Mother Theresa" between 2010 and 2013 [Table-1]. During ICU stay 307 patients (31.9%) have had ICU-acquired infections, 508 patients (52.8%) have had complications, ICU mortality rate was 31.9% (307 patients). The prevalence of malnutrition at the time of ICU admission was 62.5% (602 patients).

Table 1- Characteristics of study patients

Characteristic	N (Percentage)
Male gender	548 (56.9%)
Age*	60.82 ± 16.16 (18-92)
>60 years	210 (21.8%)
>70 years	346 (35.9%)
APACHE II score*	17.17±5.52 (5-32)
ICU days*	9.0 ± 8.1 (4-62)
Days on mechanical ventilation*	2.0 ± 4.23 (0-25)
Emergency admission	303 (31.5%)
Reason for ICU Admission	
Surgical	
• Trauma	21 (2.18%)
• Post-operative	673 (69.8%)
Medical	
• Cardiovascular	48 (4.98%)
• Respiratory	87 (9.03%)
• Neurologic	60 (6.23%)
• Sepsis	21 (2.18%)
• Other	53 (5.5%)
ICU Duration of Stay	
≤ 7 days	519 (53.9%)
>7 days	309 (32.1%)
>14 days	80 (8.3%)
>21 days	55 (5.7%)

* Data are presented as Mean ± Standard Deviation (range)

Table 2- The results of multivariate analysis of significant risk factors for mortality

Risk factors	All patients (n/%) 963	Survivors (n/%) 556 (68.1)	Non-survivors (n/%) 307 (31.9)	OR	95% CI	p-value
Age ≥ 60 years	566 (57.7)	363 (64.1)	193 (35.9)	1.72	1.29-2.29	0.0002
Malnutrition	602 (62.5)	392 (65.2)	210 (34.8)	1.91	1.41 - 2.58	<0.0001
APACHE II score ≥ 15	610 (63.3)	375 (61.5)	235 (38.5)	3.46	2.48-4.83	<0.0001
ICU LOS >14 days	135 (14.0)	64 (47.4)	71 (52.6)	3.1	2.14-4.50	<0.0001
Presence of ICU-acquired infection	307(31.9)	194 (63.2)	113 (36.8)	1.58	1.18-2.12	0.001
Presence of organ failure	231 (23.9)	119 (51.5)	112 (48.5)	2.95	2.16-4.01	<0.0001
Complications	508 (52.8)	314 (61.8)	194 (38.2)	2.34	1.75-3.12	<0.0001

Table 3- Significant risk factors for ICU-acquired infection, complications and ICU LOS > 14 days.

	ICU-Acquired Infection		Complications		ICU LOS > 14 Days	
Risk factors	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age ≥ 60years	1.64	1.06-2.52	1.28	0.99-1.66	2.23	1.48-3.34
Malnutrition	2.5	1.84-3.40	6.53	4.87-8.76	3.78	2.32-6.14
APACHE II score ≥ 15	1.8	1.34-2.42	2.35	1.80-3.08	1.63	2.23-5.90
Days on ICU	1.21	1.17-1.25	1.07	1.04-1.09		
Days on mechanical ventilation	1.31	1.25-1.38	1.16	1.11-1.22	4.46	3.45-5.76
Urgent hospital admission	2.82	2.11-3.75	1.73	1.31-2.29	2.3	1.59-3.33
Cumulated energy deficits	2.59	2.20-3.05	1.2	1.05-1.37	3.96	3.20-4.91
Day of start of nutritional support	1.35	1.23-1.48	1.28	1.14-1.43	1.1	1.04-1.17
*p < 0.05						

The results of multiple regression analysis adjusted for confounders estimating the risk factors ($p < 0.05$) for mortality, ICU-acquired infection, complications and ICU LOS > 14 days are given in tables [Table-2] and [Table-3].

Other independent risk factors for mortality were mechanical ventilation (OR = 1.87, 95% CI: 1.50-2.33), and cumulated energy deficits during ICU stay (OR = 1.25, 95% CI: 1.09-1.44).

Mortality was not related with the presence of malignant disease, urgent hospital admission or the day of start of nutrition support after ICU admission.

There were 135 patients with a prolonged ICU stay of > 14 days, forming 14% of the study group. Multivariate logistic regression analyses found that other risk factors for ICU LOS longer than 14 days ($p < 0.05$) were also presence of ICU-acquired infection (OR = 6.90, 95% CI: 4.62-10.30), presence of complications (OR = 4.50, 95% CI: 2.87-7.06), and presence of organ failure (OR = 3.43, 95% CI: 2.35-5.01).

Discussion

The ICU mortality of adult patients in the present study was 31.9%, which is higher than findings reported from the USA, Canada, and Japan (17-25%) [14]. This study sought to determine risk factors associated with ICU mortality that might be modified, to improve quality of care and patient outcomes. Multivariate analysis indicated that age above 60 years, high APACHE II score, mechanical ventilation, nosocomial infection, malnutrition and cumulated energy deficit were independently associated with ICU mortality.

In our study age was a risk factor for mortality [15] and for ICU infection, and this finding was in agreement with previous studies [16-18].

The APACHE II score was initially developed for predicting the risk of death in an ICU population [7]. In our study, as in other studies, high APACHE II score was a statistically significant risk factor for complications, mortality [17-19] and nosocomial infections [18-21].

In the present study we found that mechanical ventilation was correlated with infections, complications and mortality. The need for mechanical ventilation is associated with respiratory failure, an important risk factor for death in the ICU that has already been described in both observational and interventional studies [22,23].

The mortality rate in the group of patients with complications was 38.2%, as in other studies, patients with complications have higher mortality than patients without complications [24-26].

In the present study, infection was an important complication in patients admitted to the ICU and was found at a higher rate than that described in the literature [27-29].

The impact of ICU infections on hospital mortality is controversial. Previous studies have reported various ICU infections to be independent risk factors for hospital mortality [17,30-32]. In a multicenter study, the ICU mortality rate of infected patients was more than twice that of non-infected patients [27]. Our results support the findings of ICU-acquired infections increasing hospital mortality and the length of ICU stay [27].

The prevalence of 62.5% malnutrition in medical and surgical patients staying for more than four days in intensive care unit confirms the severity of this problem. A recent review of the world literature found that in 20 studies since 1990 the mean malnutrition rate in the hospital was 41.7% [33]. In another study the prevalence of malnutrition in the patients of the intensive care unit was as high as 47.6% on admission, using NRS 2002 method [34]. Similarly to previous studies have shown the impact of nutritional status on morbidity, mortality, LOS, we were able to demonstrate that malnourished patients in an intensive care unit have a poorer prognosis and survival [35].

The present study as other studies Villet, et al. [36], confirms that negative energy balance cumulated during inadequate nutrition support was associated with a higher rate of infections, complications, mortality, and longer ICU stay. Attempting to meet caloric targets may be associated with improved clinical outcomes in critically ill patients [37].

In several studies [38,39] the mortality of patients with ICU admissions lasting 14 days or longer was estimated to be nearly 50%, in the present study was 52.6%, also these patients require a significant proportion of resources [39-41]. Prolonged hospitalization and clinical complications generate increased costs. These costs place an even greater burden on the public health care, which already works close to its limit. This problem can be resolved, in the case of undernourished patients, using the tools and resources that are currently available within the hospitals themselves, e.g. by screening patients for malnutrition and treating appropriately with nutritional support [42]. Baue, et al. [43] suggested that better intensive care is helping critically ill patients survive, and that the key to avoiding multiple organ failure is prevention [43].

The present study has some limitations. One possible limitation would be that the study was conducted in a single center. As a tertiary center, our ICU receives referrals of complicated medical and surgical cases with high levels of severity of illness. Also we have not studied all the factors that might have a significant effect on clinical outcome. Other independent determinants of patient outcome in addition to clinical variables, such as specific structures and process qualities of an ICU, should be considered [44].

Conclusion

The risk factors for complications, longer ICU stay and mortality

were age above 60 years, high APACHE II score, nosocomial infection, mechanical ventilation, malnutrition at ICU admission and cumulated energy deficit. Knowing the risk factors can be improved patient care, optimize resource planning and may decrease health care costs.

However, because the presence of severity of illness and age are not modifiable factors, increased emphasis on the control of potentially modifiable factors such as nosocomial infection, malnutrition and cumulated energy deficit is particularly important. The results of this study indicate the importance of preventable measurements and early detection and treatment of infection in ICU population, especially in patients with urgent hospital admission.

Our findings suggest the need for implementation of Nutritional Risk Screening and Guidelines for nutrition support in critically ill patients, in order to improve the clinical outcome of them.

As the budget for the ICU is limited, a major problem remains underestimation of nutritional support and consequently an inappropriate nutrition support. Evidence of the impact of malnutrition and energy deficit in clinical outcome can encourage policymakers about the importance of investing on nutritional support. Similarly, measures to prevent nosocomial infections are important, although the expenses on preventable measures seem unnecessary and irrelevant in the conditions of restricted resources.

Abbreviations

ICU: Intensive care unit

APACHE II: Acute Physiological and Chronic Health Evaluation

US: United States

USA: United States of America

COPD: *Chronic obstructive pulmonary disease*

NRS 2002: Nutritional Risk Screening 2002

ICU LOS: Length of Intensive Care Unit stay

BMI: Body mass index

ESPEN: European Society for Clinical Nutrition and Metabolism

SOFA: Sequential Organ Failure Assessment

SD: Standard deviation

OR: Odds ratio

CI: Confidence interval

ICU-acquired infections: nosocomial infections in the intensive care unit

Author Contributions

VSH: collected data, analyzed data, interpreted data, provided conceptual advice drafting the article, wrote the paper; FK: analyzed data, interpreted data; MK: collected data, wrote the paper, AÇ: collected data, wrote the paper, IO: revised the paper critically for important intellectual content. Each author approved the final version for publication.

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