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## RESEARCH ARTICLE

## SYMPTOMATIC HETEROTOPIC OSSIFICATION: INCIDENCE AND RISK FACTORS OF A MUSCULOSKELETAL COMPLICATION IN A GENERAL INTENSIVE CARE UNIT

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## Abstract

**Background:** Heterotopic ossification is a musculoskeletal complication in patients in intensive care unit which expects to impair their mobility and quality of life after discharge. The aim of the study was to examine the incidence and the risk factors of heterotopic ossification in critically ill patients.

**Methods:** One hundred-ninety seven consecutive patients evaluated through clinical and laboratory screenings for heterotopic ossification upon admission and discharge and 123 of them were eligible for the study. Symptomatic heterotopic ossification was confirmed to 9 patients (7.31%) by means of ultrasonography and radiography. Many risk factors examined by logistic regression such as age, admission of Glasgow Coma Scale score, length of stay in intensive care unit, duration of mechanical ventilation, duration in Venturi mask and in mask tracheostomy, days in coma, traumatic and non-traumatic brain injury, increased intracranial pressure monitoring, autonomic dysregulation and days in respiratory alkalosis.

**Results:** The risk factors that predict heterotopic ossification were: age, duration of mechanical ventilation, respiratory alkalosis, days in coma, admission of Glasgow Coma Scale score, increased intracranial pressure monitoring, autonomic dysregulation, and non-traumatic brain injury. In multivariate analysis were found significant the autonomic dysregulation, the respiratory alkalosis, the increased intracranial pressure monitoring and the duration of mechanical ventilation ( $F=17.44$ ,  $p<0.00$ ).

**Conclusions:** The incidence of symptomatic heterotopic ossification appears to be significant in a general intensive care unit. A few factors seem to predict the occurrence of it, confirming previous studies. Larger studies are needed to be done for better prevention and early identification of this frequent musculoskeletal complication in critical ill patients.

**Key words:** : Incidence, prevention, risk factors, heterotopic ossification, intensive care unit.

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## INTRODUCTION

Acquired heterotopic ossification (HO) is the formation of trabecular bone there where normally does not exist, in soft tissues around a large joint of the skeleton. HO is a well-recognized musculoskeletal complication in patients in intensive care unit (ICU).<sup>1</sup>

The incidence of HO in patients that are mechanically ventilated, with traumatic brain injury, is referred to be about 13%<sup>2,3</sup> and about 21.9% after spinal cord injury.<sup>4</sup> It is expected to occupy more than one joints, referred as multi-site HO, and it is presented with a bilateral symmetry.<sup>5</sup> The early clinical diagnosis of HO is difficult because in the inflammatory stage, the signs such as, swelling erythema and warmth of the affected joint, are non-specific.<sup>6</sup> Thus, the very first signs that may be detected by a physiotherapist are the limitation of joint's range of motion and pain. There is also referred a sign of locking at the end of the joint's motion.<sup>7</sup> Another study showed that the passive range of motion of hip and elbow in patients with HO had been reduced statistically significant, while the pain of hip and elbow was significantly increased.<sup>8</sup>

Regarding the diagnosis of HO, radiography is fast, cheap, first line modality to confirm clinically suspected HO, but they allow detection approximately 4–5 weeks after the appearance of the clinical signs.<sup>5,9</sup> The bedside ultrasonography is a safe, cheap, useful and more sensitive tool at the early phase in diagnosis of HO without been necessary the transportation of critically ill patients,<sup>1,11</sup> but it has strongly been associated with the operator's expertise.<sup>9</sup>

Research has investigated the incidence and risk factors of the HO in ICU patients. Studies have incupated neuromuscular blockage interfering in the occurrence of HO in patient with acute respiratory distress syndrome.<sup>12</sup> Another risk factor widely discussed as contributing to HO triggering is mechanical ventilation.<sup>13</sup> Furthermore, coma duration and autonomic dysregulation have also been referred as risk factors for the development of HO.<sup>2</sup> A recent study by Citak et al.,<sup>14</sup> showed that patients with complete spinal cord lesions had greatest risk for HO development. There was no correlation between age, sex, race, or length of hospital stay in the aforementioned study. Sullivan et al.,<sup>15</sup> reported that risk factors for HO in pa-

tients with a SCI include the severity and the level of the SCI. Spasticity, period of intubation, multiple injuries were risk factors for the TBI, while in the SCI group, the multiple pressure ulcers appeared the most significant risk factors.<sup>16</sup> HO rarely has been referred to dominate in male gender in young age.<sup>5</sup> Other risks factors significantly associated with HO, after elbow fracture surgery, were compound fracture fracture-dislocation and longer time to surgery.<sup>17</sup>

The development of HO leads to a functional deficit, affecting patients' mobility and morbidity after their ICU discharge.<sup>18</sup> It results in longer rehabilitation length of stay, so it increases the hospital costs. Also, it affects basic daily activities such as walking and standing and it leads to lower functional scores in kinetic activities and quality of life.<sup>2</sup> Therefore, the post intensive care syndrome which describes the disability that remains in the surviving the critical illness, may also contain this pathological musculoskeletal condition. Due to the great importance of the functional status and quality of life during and after the ICU stay, HO's early detection and risk factors are necessary to be thoroughly investigated. Thus, the **aim** of the present study was to examine the incidence and the risk factors associated with the development of symptomatic HO in critical ill patients in a general ICU.

## MATERIAL AND METHODS

### *Participants*

This is a prospective study. All patients consecutively admitted to a general ICU were enrolled in the study, if they met the following inclusion criteria: (a) aged 18 to 75 years, (b) mechanical ventilation > 72h, (c) length of stay in ICU at least 5 days. The exclusion criteria were: (a) previous HO, (b) end-stage disease, (c) septic-arthritis, osteomyelitis, and (d) pregnancy. Our general ICU receives different pathologies of patients, such as neurological/neurosurgical, respiratory, burn and general surgical patients. Treatment of patients of the ICU was according to the acute trauma life support protocol and was based on international guidelines for the management of critically illness patients. All the included patients were followed until their discharge from ICU and/or high dependency unit. The duration of screening was 6 months. The study was approved by the

research ethics committee board of the hospital. The relatives of the participants were informed about the procedures of the study and signed a written informed consent form proposed by the scientific team of the Hospital.

#### *Assessment tools*

A form included details from the medical file admission in ICU (i.e., medical history, type of injury, Glasgow Coma Scale (GCS) score, Acute Physiology and Chronic Health Evaluation II, sequential organ failure assessment, Simplified Acute Physiology Score III, fractures etc.) and every day stay in ICU (i.e., mechanical ventilation, fever, autonomic dysregulation, physiotherapy/mobilization, drugs, etc.) completed every day by a team of physiotherapists and a doctor.

The assessment of elbow, shoulder, knee, and hip joints' passive range of motion, edema, and swelling was done by a physiotherapist every week. Blackman et al.,<sup>19</sup> reported the criteria which described the autonomic dysregulation. Particularly, symptoms of autonomic dysregulation were defined as paroxysmal increase in heart rate ( $>120/\text{min}$ ), respiratory rate ( $>24/\text{min}$ ), temperature ( $>38.5^\circ\text{C}$ ), systolic blood pressure ( $>160\text{ mm Hg}$ ), with decerebrate or decorticate posturing, profuse sweating and increased muscle tone. Autonomic dysregulation was defined as present when a patient had 5 of these 7 symptoms for at least 3 days and other conditions (such as infection) were not present. The duration of mechanical ventilation was measured as the time entering the ICU in ventilator until continuous spontaneous respiration. When a patient was weaned from ventilation (and he was at least 12 hours in spontaneous respiration), the hours of spontaneous respiration between ventilated moments were deducted from the ventilation time. When a patient was re-intubated and mechanically ventilated, this new period was added to the ventilation time.

#### *Outcome variables*

All patients, after their admittance to ICU, were detected to the development of symptomatic HO which results in the clinical symptoms of pain, erythema and/or swelling of the affected joint, and/or limitation in range of motion. Clinically suspected HO was confirmed objectively by ultrasonography and radiog-

raphy examined by a qualified radiologist. The classification of HO was based on the clinical, ultrasonographical and radiographical results, regarding the system German Cooperative Group on Radiotherapy on Benign Diseases.<sup>20</sup>

#### *Independent variables*

The independent variables examined as potential risk factors included: age, admission of GCS score, length of stay in ICU, duration of mechanical ventilation, duration in Venturi mask and in mask tracheostomy, days in coma, traumatic and non-traumatic brain injury, intracranial pressure (ICP) monitoring, autonomic dysregulation and days in respiratory alkalosis.

#### *Statistical analysis*

All data were filed by using the SPSS-data package (SPSS Inc, Chicago, Illinois). Two groups were distinguished patients with and without symptomatic HO. *T*- tests were performed between the two groups in age, admission GCS score, length of stay in ICU, duration in mechanical ventilation and in Venturi mask, and respiratory alkalosis. The independent variables of days in coma, traumatic and non-traumatic brain injury, intracranial pressure monitoring, autonomic dysregulation were not normally distributed; therefore, the differences between the two groups were assessed by the Mann-Whitney U test and  $\chi^2$  using an  $\alpha$  level of  $P < 0.05$  to indicate significance. Also, logistic regression and multivariate regression analyses were performed to predict the development of symptomatic HO in the general ICU.

## **RESULTS**

One hundred-ninety seven consecutive patients evaluated through clinical and laboratory screenings for HO upon admission and discharge from the ICU (Figure 1). Seventy-four patients were excluded from the study, particularly: (a) 44 (22.10%) patients due to  $< 5$  days in ICU, (b) 29 (14.60%) patients due to age  $< 18$  and  $> 78$  years old and (c) 1 (0.50%) patient due to final stage disease. One hundred twenty-three were eligible (75 men, 48 women, age  $52.77 \pm 14.99$  years, length of stay in ICU  $27.35 \pm 22.14$  days, mechanical ventilation  $21.77 \pm 19.84$  days).

Symptomatic HO was confirmed to 9 patients (7.31%) with a mean diagnosed of 65 days (SD=13.97, Md=67, Range=46) (Table 1). All the 9 patients, who developed HO, had brain injury, particularly the 33.30% of patients had TBI (3 patients of 9) and the 66.70% (6 patients of 9) non TBI (e.g., 22.20% stroke, 22.20% brain tumor, 22.20% encephalopathy). HO was located mainly in the hip (88.90%), shoulder (33.30%), knee (22.20%) and elbow (11.10%) joint. HO was detected in 12 hips, 4 shoulders, 2 knees, and 1 elbow (total of 19 heteropic ossifications). The 55.6% of the patients appeared HO in most of one joints. The mean time of HO diagnosis following their admission day in ICU was  $65 \pm 13$  days (Md=67, Range=46). None of the patients were surgically treated for the HO during the study period. All patients with HO received nonsteroidal anti-inflammatory drugs and physiotherapy as treatment for HO.

Table 2 showed the significant differences between the two groups in regard to the independent variables. Also, the median duration in mask tracheostomy ( $U=140.50$ ,  $p=0.00$ ), in people with HO was 100.39 compared to 57.27 in the group without HO. Furthermore, the  $\chi^2$  values of the independent variables of TBI ( $\chi^2=14.26$ ,  $df=3$ ,  $p=0.00$ ), non TBI ( $\chi^2=12.40$ ,  $df=5$ ,  $p=0.03$ ), ICP monitoring ( $\chi^2=5.66$ ,  $df=1$ ,  $p=0.01$ ) and autonomic dysregulation ( $\chi^2=21.33$ ,  $df=1$ ,  $p=0.00$ ) were significant. No significant differences were noted in regard to other independent variables.

The results of the univariate logistic regression showed risk factors that predict the occurrence of HO. Particularly, the equation of the linear regression line is  $Y = -6.73 + (-0.06) \times \text{age} + 0.08 \times \text{duration of mechanical ventilation} + 0.01 \times \text{days in coma} + (-0.06) \times \text{Admission GCS score} + 0.14 \times \text{Respiratory alkalosis in days} + 4.56 \times \text{Autonomic dysregulation} + 2.92 \times \text{ICP monitoring} + 2.08 \times \text{Non-traumatic brain injury}$ . In multiple analysis, included all significant independent variables from the univariate analysis, using stepwise method, were found statistically significant the autonomic dysregulation, the duration of mechanical ventilation, the respiratory alkalosis, and the ICP monitoring ( $F=17.44$ ,  $p<0.00$ ) (Table 3). Regarding the prediction of HO, the autonomic dysregulation, the respiratory alkalosis, the presence of intracranial pressure monitoring and the duration of mechanical ventilation were the 46.60% of vari-

ance ( $R^2=0.46$ ,  $p<0.05$ ).

## DISCUSSION

Our study showed that the 7.3% of the patients of a general ICU, who stayed for more than 5 days in ICU and more than 72 hours with mechanical ventilation, developed symptomatic HO. Ultrasonography and X-ray were performed only on clinically HO. Other studies investigated the appearance of the HO in specific clinical population of ICU, such as respiratory ICU, neurological ICU, surgical ICU, etc. Particularly, previous research showed that 5% of their patients with acute respiratory distress syndrome developed HO one year after their discharge of ICU [5]. Similarly, HO appeared in 8-13% patients with TBI.<sup>2,20</sup> Recently, Dizdar et al.,<sup>21</sup> showed that clinically identifiable HO developed in 37.1% of TBI patients. Probably, the appearance of HO was underestimated in our study because patients have not been checked for HO after discharge from ICU and high dependency unit. Simonsen<sup>22</sup> reported that TBI patients' probably developed HO until 4 months, thus our patients have not been re-assessed after their discharges from ICU and high dependency unit.

The brain injury was a risk factor of the HO. All the 9 patients who developed HO had brain injury. Other studies confirm these results.<sup>1,3</sup> After TBI, neurological repercussions affect organism and bone hormonal control. Central nervous system damage is believed to activate local factors such as bone morphogenic protein or systemic factors such as prostaglandin E2, or both.<sup>23</sup> These factors could induce bone-forming mesenchymal cells to differentiate to osteoblasts in the periphery of the muscle and stimulate the formation of bone.<sup>24</sup> It is possible that the mode of injury may contribute to the mechanisms of HO formation and micro trauma may induce ossification through induction of local inflammatory responses or by releasing osteoblast-stimulating factors.<sup>16</sup> Further investigation is needed regarding the mechanisms or factors that may underlie the relationships of brain injury severity with HO.

Prolonged duration of coma, lower score of Glasgow, mechanical ventilation as well as the occurrence of autonomic dysregulation should be considered as potential risk factors. Our study showed that patients with HO stayed statistical longer in ICU in

comparison with those who did not develop HO, thus the duration in the ICU is a statistically significant risk factor. On the contrary, Citak et al.,<sup>4</sup> suggested that this variable did not predict the development of HO. The duration of the ICU is also related to the duration in mechanical ventilation.<sup>2</sup> Hendricks et al.,<sup>3</sup> found that those patients with brain injury and HO had been in mechanical ventilation longer  $22.33 \pm 13.47$  days versus  $7.25 \pm 7.78$  days than those without HO ( $z=3.68$ ,  $p<0.00$ ). Also, Van Kampen et al.,<sup>2</sup> found statistically significant longer period in mechanical ventilation in patients with TBI with HO ( $M=16.50$  days) versus those without HO ( $M=6.87$  days) ( $z=-3.05$ ,  $p=0.00$ ). Future studies with large sample size may confirm this assertion and define the interrelationship between the duration of the ICU with mechanical ventilation as risk factors of HO.

We found GCS to be a risk factor of HO. However Van Kampen et al.,<sup>2</sup> and Hendricks et al.,<sup>3</sup> did not find statistical correlation between HO and GCS due to the low  $GCS<8$  that patients had. Due to contradictory results, more research should be done to confirm this risk factor of HO. Also, the present study examined the days in coma as a risk factor for the development of HO. Van Kampen et al.,<sup>2</sup> found that patients with HO had statistical significant mean coma duration 15 days in comparison with 4.18 days of those without HO (Mann-Whitney  $U=199.50$ ,  $z=-3.65$ ,  $p<0.001$ ). Hendricks et al.,<sup>3</sup> reported that patients with HO sustained more severe brain injuries as this determined by days in coma, days in mechanical ventilation, diffuse axonal injury and spasticity. More research should be done to confirm this risk factor.

Furthermore, autonomic dysregulation is another risk factor that is present in the brain injury patients. Similarly, Van Kampen et al.,<sup>2</sup> and Hendricks et al.,<sup>3</sup> supported strong association in TBI patients with the development of HO (RR: 59.55, 95% CI: 8.39-422.36) in the first study and (RR: 6.11, 95% CI: 2.53-14.76) in the second study. Although the causal mechanism between autonomic dysregulation and development of heterotopic bone formation has not yet been confirmed, autonomic nervous system may play an important regulating role in bone formation in traumatic brain injury patients.<sup>25</sup>

Present results confirmed that increased ICP is a statistical risk factor of HO. These results are in agreement with Hendricks et

al.,<sup>7</sup> who found that patients with serious TBI and increased ICP developed HO (RR: 4.81, 95% CI: 1.06-21.65). The normal values varied regarding the age, pathology, clinical situation and the body position, however ICP  $>15$  mm Hg generally is pathological.<sup>26</sup> There is a need for larger multivariate studies to confirm the mechanism of this risk factor to HO development in TBI patients.

There has not been previous research in examining respiratory alkalosis as a risk factor of HO. Newman et al.,<sup>27</sup> suggested that respiratory artificial hyperventilation in severe head injured patients, in terms of reducing intracranial pressure or the independent hyperventilation, could lead to alkalosis, consequently to a pH alteration and thus change of the precipitation kinetics of calcium and phosphate salts, leading to accelerate fracture union. The exact mechanism is not clear enough. Further research should be conducted to clarify the importance of respiratory alkalosis in HO's prediction.

From the demographical characteristics, we found that the age is a risk factor of HO. The 9 patients with HO had mean age 40.89 (SD=14.49) in comparison with the group without HO ( $M=53.80$ ,  $SD=14.70$ ). These results are in agreement with Seipel et al.,<sup>5</sup> and Wittenberg et al.,<sup>28</sup> who found the incidence of HO in patients at young age of 20 to 30 years old. However, Van Kampen et al.,<sup>2</sup> Hendricks et al.,<sup>3</sup> and Citak et al.,<sup>4</sup> did not find any statistical correlation between age and HO. There is a need for larger multivariate studies to confirm the mechanism which contributes this risk factor to HO development both in traumatic brain injury and spinal cord injury patients.

Early diagnosis of HO is important because it is expected to lead in severe functional limitation, particularly over 5% of patients in ICU for an average of one year duration which has an impact in the quality of patient's life. Ultrasonography is the best investigative modality for the early identification, it's easier to perform than magnetic resonance imaging, and in the present study it has been used from an experienced radiologist after clinical suspicion. Studies suggest ultrasonography may be more specific in differentiating HO from other traumatic, inflammatory, or degenerative diseases of skeleton than bone scan. It has been shown to detect earlier than traditional radiographic studies the HO.<sup>29</sup> Indeed, in the present study, five



patients, at the time who did ultrasonography and had appeared HO, the X-ray did not show HO. Therefore the clinical significance of early detection of HO is important due to the long-lasting effects of HO on recovery.

The limitations of this study include the different pathology of patients due to a general ICU. Another limitation is the possibility of underestimating the incidence of HO due to the existence of asymptomatic HO and the absence of evaluation after ICU and high dependency unit. Replication of this research is recommended in order to obtain the profile of the patients who are susceptible to develop HO. Additional research should be conducted to evaluate the high profile patients of developing HO after 1-year of discharge of ICU. In future studies, it also would be beneficial to take preventive measures (e.g., usage of neuromuscular electric stimulation) so as to have better rehabilitation and quality of life. Even in nowadays there is poor literature according to simple interventions with direct influence in joints range of motion such as physiotherapy. Gentle passive range of motion exercises may maintain joint mobility and prevent secondary soft-tissue contractures. There is a need for randomized control trials in ICU patients to estimate the impact of early passive mobilization, with continuous passive range of motion machine, bedside cycling exercises, or passive range of motion exercises, in the development of HO. The quality of life after the ICU is a common purpose of the rehabilitation personnel, early detection and prevention of HO should be thoroughly investigated.

## CONCLUSIONS

HO is a musculoskeletal complication in patients in ICU which expects to provoke long-lasting morbidity impairing basic daily activities. The 7.3% incidence of symptomatic HO in the present study appears to be significant in a general ICU. A few factors seem to predict the occurrence of symptomatic HO such as autonomic dysregulation, respiratory alkalosis, duration of mechanical ventilation and intracranial pressure monitoring. Larger studies are needed to confirm these results for better prevention and early identification of this frequent complication in ICU.

## Abbreviations

HO: Heterotopic Ossification

ICU: Intensive Care Unit

TBI: Traumatic Brain Injury

SCI: Spinal Cord Injury

GCS: Glasgow Coma Scale

ICP: Intracranial Pressure

## Declarations

### Ethics approval and consent to participate

The study was approved by the Research Ethics Committee Board of the General Hospital of 'Evangelismos'. The relatives of the participants were informed about the procedures of the study and signed a written informed consent form proposed by the Scientific Committee of the Hospital. The publication of the results must have been anonymous.

### Consent for publication

Not applicable

### Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to the hospital regulation regarding personal data of patients but are available from the corresponding author on reasonable request.

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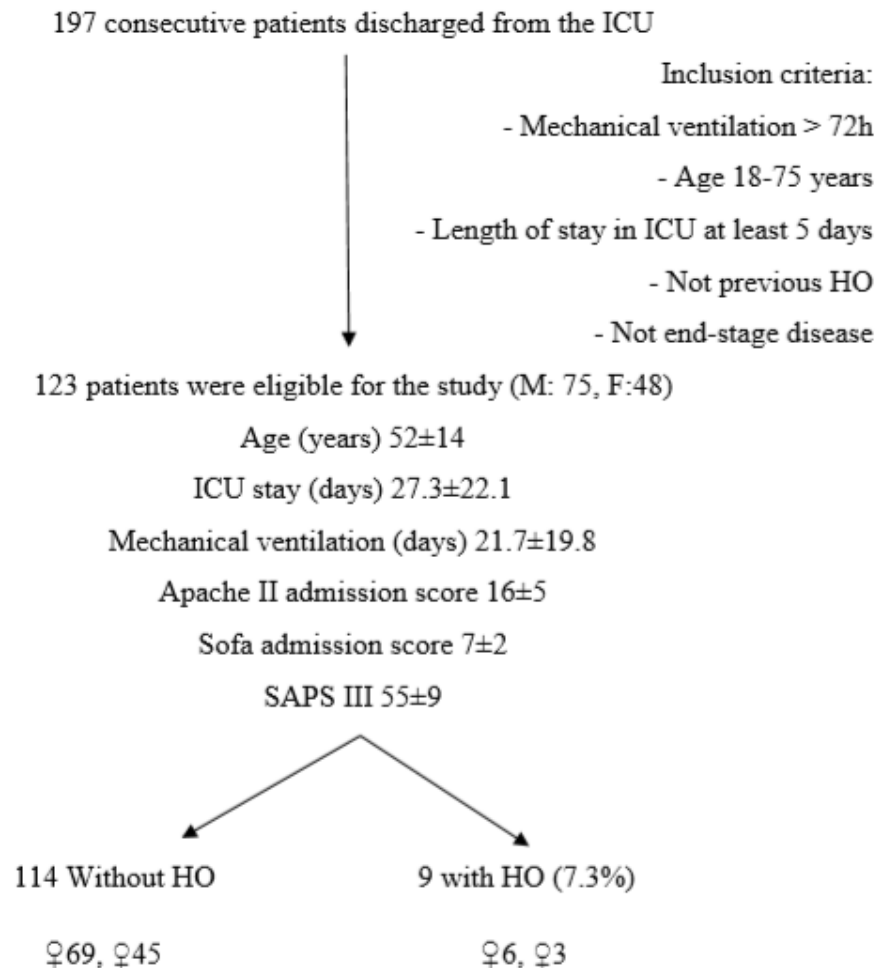
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## ANNEX

**FIGURE 1.** Flow chart of patients

**TABLE 1.** Demographic information of patients with and without HO

Characteristics	114 patients without HO	9 patients with HO
Sex	69♂, 45♀	6♂, 3♀
	Mean ± SD	Mean ± SD
Age	53±14	41±14
APACHE	17±5	20±6
SOFA	7±2	10±2
SAPSIII	56±10	50±0
ICU stay (days)	25±20	55±31
Mechanical ventilation (days)	20±17	44±37
	Frequencies (%)	Frequencies (%)
Cardiovascular failure		
Yes	15 (13.30%)	2 (22.20%)
No	98 (86.70%)	7 (77.80%)
Fractures		
Yes	23 (20.40%)	3 (33.30%)
No	90 (79.60%)	6 (66.70%)
Diabetes		
Yes	14 (12.40%)	11 (1.10%)
No	99 (87.60%)	88 (8.90%)
ARDS		
Yes	13 (11.50%)	1 (11.10%)
No	100 (88.50%)	8 (88.90%)
Cancer		
Yes	24 (21.20%)	2 (22.20%)
No	89 (78.80%)	7 (77.80%)
Kidney failure		
Yes	12 (22.60%)	1 (11.10%)
No	41 (77.40%)	8 (88.90%)

**TABLE 2.** Significances in comparisons between HO group and the group without HO

Variables	Patients with HO (n=9)		Patients without HO (n=114)		t
	M	SD	M	SD	
Age	40.89	14.49	53.82	14.68	2.54 p=.024
Length of stay in ICU	55.00	31.73	25.60	20.28	-4.00 p=.024
Admission GCS score	7.14	2.19	10.64	4.21	2.17 p=.004
Duration in Venturi mask	.22	.44	2.27	3.49	1.75 p=.000
Respiratory alkalosis	14.00	10.00	5.20	6.13	-3.84 p=.043

HO: Heteropic ossification, M: Mean, SD: Standard deviation

**TABLE 3.** Multivariate logistic regression model results of statistical variables related to development of HO

Variables	b	SE b	$\beta$	t
Intercept	1.31	.22		5.81***
Autonomic dysregulation	-.59	.10	-.46	-5.50***
Respiratory alkalosis	.01	.00	.21	2.34*
Duration of mechanical ventilation	.00	.00	.23	2.55*
Intracranial pressure monitoring	-.11	.05	-.17	-2.07*

HO: Heteropic ossification, \* $p < .05$ , \*\*  $p < .01$ , \*\*\* $p < .001$