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# OBESITY AS THE MOST SIGNIFICANT POSITIVE PREDICTIVE FACTOR FOR DEVELOPMENT FOR THE DEVELOPMENT OF ARDS IN PATIENTS WITH INFLUENCA A

## Introduction

Infection with influenca A virus can result in rapidly progressive respiratory failure, acute respiratory distress syndrome (ARDS), and death (1).

During the pandemic A virus infection, H1N1 subtype, in 2009, the authors showed a significant number of patients with severe clinical picture and necessary treatment in intensive care units (2-5). The severe form of the disease was most common with older patients with comorbidities (6).

An important risk factor for the occurrence of fatal outcome in patients with influenca A H1N1 was marked obesity (7).

The aim of our work was to examine the effect of obesity on the clinical course and the occurrence of ARDS and on the final outcome of the disease in patients with influenca A.

## Methods

We examined the patients who were treated at the Department of Infectious Diseases and Intensive Care Unit of the General Hospital Uzice, from 01.01.2006. until 31.12.2017.

Influencae A virus was diagnosed at the Institute of Immunology and Virusology "Torlak" in Belgrade by the polymerase chain reaction (PCR) from the towel of the throat and determining the titre of the IgM antibody in the serum.

Criteria for the diagnosis of ARDS were:

– acute clinical condition,

– clinical picture of respiratory damage (tachypnea > 20 min),

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– Pa02 < 6.6 kPa (50 mmHg),

– bilateral pulmonary infiltrates on the x-ray (8).

The obesity classification was performed according to the body mass index (BMI): BMI 30 to 34.9 kg/m2 indicating I degree of obesity, 35 to 39.9 kg/m2 II degree, and BMI ≥ 40 kg/m2 III degree of obesity (9).

The following data were analyzed:

– epidemiological: age, sex;

– comorbidities: diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), neurological and cardiological diseases;

– laboratory analyzes: hematological, biochemical, microbiological;

– radiography of the lungs.

## Results

A total of 405 patients with influenca A were examined. Of these, 42 (10.4%) patients had severe disease with clinical and radiographic signs of massive broncho-pneumonia. Of these, 21 (50%) patients had ARDS.

Virus influencae top A, H1N1 subtype was isolated in 15 (71.4%) patients with influenca and ARDS.

The epidemiological, clinical and laboratory results respondents are shown in Table 1.

**Table 1. Epidemiological results and comorbidities of patients with influenca and ARDS**

| Characteristics | Number of patients (%)/ N=21 | p |
|---|---|---|
| Age ≥ 65 godina | 15 (71.4) | 0.025 |
| Gender ( male) | 13 (61.9) | 0.482 |
| Comorbidities | | |
| Obesity | 18 (85.7) | <0.001 |
| Diabetes mellitus | 12 (57.1) | 0.807 |
| Cardiac disease | 9 (42.9) | 0.376 |
| Asthma/HOPD | 17 (80.9) | 0.001 |
| Neurological disease | 6 (28.5) | 0.029 |
| Bacteriological isolates (sputum, aspirate, tube erosion) | 14 (66.7) | 0.494 |
| Leukocytosis >15x$10^9$/L | 13 (61.9) | 0.462 |
| C reactive protein >5mg/l | 18 (85.7) | 0.001 |

p – statistical significance between the number of patients with the mentioned parameter in relation to the total number of patients with ARDS.

The study showed that patients with ARDS were significantly older than 65 years of age, were obese and had asthma/COPD.

Table 2 shows the results of the univariant linear regression of age, obesity and asthma/HOPD in relation to ARDS.

**Table 2. Age and comorbidities of patients as predictors of ARDS**

| Age and comorbidities (independent variable) | ARDS (dependent variable) | | |
|---|---|---|---|
| | B | S.E. | P |
| Age ≥ 65 years | 0.229 | 0.094 | 0.016 |
| Obesity | 0.45 | 0.09 | 0.000 |
| Asthma/HOPD | 0.307 | 0.101 | <0.001 |

Multivariate analysis ndicated obesity as the most significant positive predictive factor for development for the development of ARDS in patients with influenca A.

Obesity of I degree was 6 (35.3%), II degree was 7 (41.2%), III degree was 4 (23.5%) patients.

The disease had a fatal outcome in 12 (57.1%) patients. 9 (75%) of wich were obese. In 66.7% of these patients obesity was type II.

Table 3 shows the results of the analysis of the degree of obesity, ages over 65 years, and the subtype of H1N1 influenca A virus in relation to the lethal outcome.

**Table 3. Age, obesity and subtype H1N1 viruses in patients with fatal outcome**

| Characteristics | Fatal outcome (%)/N=12 | p |
|---|---|---|
| Age > 65 godina | 8(66.7) | 0.586 |
| Obesity | 9 (75) | 0.023 |
| Podtype H1N1 | 10(83.3) | 0.001 |

p – statistical significance between the number of patients with the mentioned parameter in relation to the total number of patients with a fatal outcome.

The study showed significant presence of the H1N1 influenca A virus subtype and obesity in patients with a fatal outcome due to influenca complicated by the development of ARDS.

## Discussion

Obesity is one of the most common diseases in the world today (9). It increases the likelihood of many other diseases, such as cardiac disease, diabetes mellitus, obstructive sleep apnea, some types of cancer, asthma (10). Research has been de-

monstrated the influence of obesity on the reduction of the immune response of the organism after influenca vaccine (11).

By analyzing the socio-demographic characteristics of our patients with influenca A, we noticed a significantly higher ARDS presence in people older than 65 years. The analysis of patients by gender did not indicate significant differences. Other authors had similar conclusions. In their studies, the elderly were more likely to have ARDS, with no significant difference in gender (6).

A significant majority of our patients had obesity and asthma or HOPD, similar to other studies. Lui and associates pointed to obesity as a significant factor in fatal outcome in patients with influenca caused by type A H1N1 virus (7). Most of our respondents had a subtype of H1N1 influenca A virus, and 75% of patients with a fatal outcome were obese, and we consider these facts to be matched. The same authors pointed to asthma as a significant joint disease (7). Our results are also in line with this research.

Our study did not show a significant presence of associated bacterial bronchospemmonia on the percentage of bacterial isolates. However, biochemical parameters of bacterial infection were present in most subjects, and it can be assumed that bacterial superinfection was also significantly present. The lack of isolates that could prove this conclusion can be explained by the antibiotic therapy most patients received ambulatory, from the beginning of the disease.

Other researchers consider that obese people have a significantly higher risk of disease and mortality from influenca viruses, too (12).

The World Health Organization pointed to obesity as an independent factor in the occurrence of complications in influenca (13).

The effect of obesity on the worsening of clinical course of influenca and the occurrence of ARDS can be explained by the effect on the cellular immune response. It is necessary that the dendritic cells present influenca virus and stimulate the activation of influenca-specific CD4 + and CD8 + T cells to an adequate immune response. CD4 + cells influence the synthesis and secretion of cytokines, activation, and cytotoxic functions of CD8 + cells and the synthesis of specific anti-inflammatory antibodies (14).

The study showed that obese people have lower levels of CD4 + and CD8 + cells, lower expression of CD69 and CD28 receptors to participate in activation and proliferation of T cells. Also, the expression of CD40 molecules and interaction with CD40L on dendritic cells was reduced (11). This is the way in which a cellular and humoral immune response to the influenca virus is disrupted.

## Conclusion

In patients with influenca in whom the disease is complicated by ARDS, the most common cause of influenca was the influence A subtype H1N1. This subtype of the virus was most common in patients with a history of fatal outcome. Patients with

influenca A were most commonly aged over 65 years of age. A significant number of these patients had asthma or chronic obstructive pulmonary disease. The most significant factor that contributed to the development of ARDS was obesity. In patients with fatal outcomes, obesity was also an important factor for such outcome.

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