Diagnostic value of cystatin C in patients with drug-resistant pulmonary tuberculosis receiving palliative care

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To date there are no data on the study of heart failure early diagnostic criteria in patients with pulmonary drug-resistant tuberculosis (DRTB) available in the literature. The purpose of the work is to determine the level of serum cystatin C in patients with pulmonary DRTB receiving palliative care and to establish the diagnostic value of this indicator in the early diagnosis of heart failure.

Materials and methods. Patients of the main group received palliative care were divided into 2 groups depending on the body mass index (BMI): the main group 1 consisted of 26 patients with BMI ≤18.1 kg/m², the main group 2 was composed of 26 patients with BMI >18.1 kg/m². The control group included 29 patients who received antimycobacterial therapy by category 4 according to the drug resistance profile. The level of serum cystatin C was measured by an enzyme-linked immunosorbent assay (ELISA) using the kit "Human Cystatin C ELISA BioVendor Research and Diagnostic Products" (ng/ml; Czech Republic). The serum level of TNF-α was studied by ELISA in a reader Sirio S using the kit “Bender MedSystems GmbH” (Austria), (pg/ml). The results of the study were processed on a personal computer using statistical software package Statistica, version 13 (Copyright 1984–2018 TIBCO Software Inc. All Rights reserved. License No. JPZB041382130ARCH10-J).

Results. In patients with pulmonary DRTB receiving antimycobacterial therapy, the level of cystatin C exceeds the upper limit of the normal reference values, and in palliative care DRTB patients with BMI >18.1 kg/m² it is 10.4 % higher than in pulmonary DRTB patients receiving antimycobacterial therapy. At the same time, in patients with pulmonary DRTB receiving antimycobacterial therapy, an increase in serum cystatin C level is significantly associated with a decrease in serum TNFα levels and an increase in BMI. In palliative care patients with DRTB and BMI >18.1 kg/m², an increase in serum cystatin C levels significantly depends directly on a decrease in serum TNFα. And in palliative care patients with pulmonary DRTB and BMI ≤18.1 kg/m², a decrease in cystatin C level significantly depends directly on a decrease in BMI and inversely depends on an increase in serum TNFα level, which leads to a significant decrease in the overall quality of life score and heart failure progression.

Conclusions. In palliative care patients with DRTB and BMI >18.1 kg/m², increased level of cystatin C can serve as an early marker of heart failure development. In palliative care patients with DRTB and BMI ≤18.1 kg/m², low level of cystatin C can serve as a marker of secondary cardiovascular disease development and heart failure progression.
In many countries of the world, there is palliative and hospice care for palliative patients and their family members, which ensure an adequate quality of life (QoL), including palliative care patients with tuberculosis [1]. Nowadays in Ukraine, patients with drug-resistant pulmonary tuberculosis (DRTB) in need of palliative treatment are not provided with the necessary palliative care. Also in Ukraine, there is a lack of regulatory documents demonstrating the management tactics of such patients.

It has been established that one of the causes of death in patients with pulmonary DRTB is heart failure with underlying cachexia [2]. In the available literature, there are no data on the study of indicators for early diagnosis of heart failure in patients with pulmonary DRTB receiving palliative treatment.

Currently, studies of serum cystatin C as an early marker of heart failure and data on the progression of this indicator in chronic course of the disease are being conducted [3–7].

Thus, diagnostic value of serum cystatin C determination in patients with pulmonary DRTB receiving palliative treatment would allow for timely diagnosis of heart failure, provide an opportunity to prescribe adequate pathogenetic therapy, thereby slowing the progression of heart failure and improving the quality of life and life expectancy in these patients.

The purpose
The purpose of the work is to determine the level of serum cystatin C in patients with pulmonary DRTB receiving palliative care and to establish the diagnostic value of this indicator in the early diagnosis of heart failure.

Materials and methods
A total of 81 patients with pulmonary DRTB were examined in the Zaporizhzhia Regional Hospital and the Specialized Tuberculosis Hospital at the Sofiyevska Penitentiary Colony (No 55) of the Ministry of Justice of Ukraine in the Zaporizhzhia Region. All patients (100 %) were male.

Considering the data we obtained [8], the patients of the main group (52 patients) received palliative treatment were divided into 2 groups depending on the body mass index (BMI). The main group 1 consisted of 26 patients with BMI ≤18.1 kg/m² (the mean age was 38.3 ± 2.3 years), the main group 2 was composed of 26 patients with BMI >18.1 kg/m² (mean age 40.5 ± 2.3 years). The control group included 29 patients who received anti-mycobacterial therapy (AMTB) by category 4 according to the drug resistance profile in compliance with the Unified Clinical Protocol of Medical Care “Tuberculosis” (the Order of the Ministry of...
Health of Ukraine № 620 of 04.09.2014) [9], the mean age was 41.3 ± 1.8 years.

The level of serum cystatin C was measured by an enzyme-linked immunosorbent assay (ELISA) using the kit “Human Cystatin C ELISA BioVendor Research and Diagnostic Products” (ng/ml; Czech Republic). The serum level of TNF-α was studied using ELISA in a reader Sirio S using the kit “Bender MedSystems GmbH” (Austria), (pkg/ml).

The quality of life (QoL) was assessed using the MOS SF-36 questionnaire (St. Petersburg, RF, 1998). The QoL assessment was based on a summary total (ST) QoL indicator, which included all scales (1–8) of the questionnaire (relative units, rel. un.).

To calculate the body mass index (BMI), a New Body Mass Index (New BMI) calculator (kg/m²) was used.

Renal function was not impaired in all patients enrolled in this study. The glomerular filtration rate (GFR) was within the normal range.

All patients signed an informed written consent to take part in the study.

The study results were processed on a personal computer using the statistical package of the licensed program Statistica, version 13 (Copyright 1984–2018 TIBCO Software Inc. All rights reserved. License No. JPZB041382130ARCN10-J). The Shapiro–Wilks test was used for normal-distributed quantitative data. Descriptive statistics including median and interquartile range – Me [Q25; Q75] were calculated to express the variables, which were not normally distributed. Differences between values were compared using Mann-Whitney test. All tests were bilateral and the chosen statistically significant level was P < 0.05. Correlation analysis was performed using the Pearson correlation coefficient (r).

**Results**

The reference values for cystatin C according to the manufacturer’s protocol were in the range of 570–1790 ng/ml. We found that the serum level of cystatin C on admission to the hospital was 1272.6 (809.9; 1497.1) ng/ml in patients of the main group 1 which was significantly 1.6 times (P < 0.05) lower than in the main group 2 – 2100.4 (1741.9; 2678.4) ng/ml and 1.4 times than in the control group – 1880.5 (1658.9; 2384.3) ng/ml (Fig. 1). There was no significant difference in cystatin C levels between the main group 2 and the control group.

At the same time, serum TNFα levels were found to be 7.7 times higher in patients of the main group 1 620 (290; 985) pkg/ml in comparison with the control group and the main group 2 80 (60, 120) pkg/ml and 80 (45; 80) pkg/ml, respectively (P < 0.05), indicating a high activity of the specific inflammatory process in these patients.

The BMI level in patients in the main group 1 was 1.2 times lower 16.8 (16.0; 17.2) kg/m² than that in the control and in the main group 2 – 20.8 (18.9; 23.0) kg/m² and 21.2 (19.8; 22.0) kg/m², respectively (P < 0.05), demonstrating the prevalence of underweight patients which is an unfavorable factor associated with cachexia progression.

The ST QoL of patients in the main group 1 was 1.6 times lower 40.4 (37.2; 48.8) rel. un. than that in the control group 66.9 (51.3; 72.1) rel. un. and 1.4 times than that in the main group 2 58.1 (49.8; 66.8) rel. un. (P < 0.05). At the same time, the ST QoL in the main group 2 patients was 1.2 times lower 58.1 (49.8; 66.8) rel. un. than that in the control group 66.9 (51.3; 72.1) rel. un. (P < 0.05).

Evaluating the correlation between cystatin C and TNFα, BMI and ST QoL, it was found that in patients of the main group 1, a decrease in the serum level of cystatin C significantly depended directly on a decrease in the BMI (r = 0.75; P = 0.001) and inversely depended on an increase in the serum TNFα level (r = -0.98; P = 0.001), which significantly directly declined the ST QoL (r = 0.53; P = 0.01).

In the main group 2 patients, an increase in the serum level of cystatin C significantly correlated with a decrease in the serum TNFα level (r = 0.61; P = 0.001).

In the control group, there was a weak inverse correlation between an increase in the serum cystatin C level and a decrease in the serum TNFα level (r = 0.36; P = 0.05) and a direct correlation between increase in the cystatin C level and BMI (r = 0.65; P = 0.01).

**Discussion**

According to literature [3–7], elevated serum levels of cystatin C are associated with a high risk of cardiovascular diseases resulting in cardiac insufficiency development. V. V. Velkov (2011) [4] noted that the serum level of cystatin C significantly depends directly on an increase in BMI and patient’s age. According to our data, in patients with pulmonary DRTB receiving AMBT, the level of cystatin C exceeds the upper limit of the normal reference values, and in palliative care DRTB patients with BMI >18.1 kg/m² it is 10.4 % higher, than that in patients with pulmonary DRTB receiving AMBT. At the same time, in patients with pulmonary DRTB receiving AMBT, elevated serum level of cystatin C is significantly associated with a decrease in serum TNFα level and an increase in BMI. In palliative care patients with DRTB and BMI >18.1 kg/m², an increase in the levels of cystatin C also significantly depends on a decrease in the serum TNFα levels. And in palliative care patients with pulmonary DRTB and BMI ≤18.1 kg/m², a decrease in cystatin C level significantly depends directly on...
a decrease in BMI and, the reverse is true for an increase in the serum level of TNFα, thus greatly contributing to a decrease in the ST QoL.

Conclusions

1. In palliative care patients with pulmonary DRTB and BMI index >18.1 kg/m², elevated level of cystatin C can serve as an early marker of heart failure development.

2. In palliative care patients with pulmonary DRTB and BMI index of ≤18.1 kg/m², low level of cystatin C can serve as a marker of secondary cardiovascular disease development and heart failure progression.

Prospects for further research. Development of pathogenetic therapy for cystatin C correction depending on BMI of palliative care patients with pulmonary DRTB would help slow heart failure progression and to improve the quality of life and life expectancy in these patients.

Conflicts of interest: authors have no conflict of interest to declare.

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