PREDICTION OF CARDIOVASCULAR RISK AMONG MALE PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS IN VOJVODINA, SERBIA – A SINGLE CENTRE STUDY

PROCENA KARDIOVASKULARNOG RIZIKA KOD MUŠKARACA INIFICIRANIH VIRUSOM HUMANE IMUNODEFICIJENCIJE U VOJVOĐINI, SRBIJA – MONOCENTRičNA STUDIJA

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Abstract

Introduction. Human immunodeficiency virus infection is a disease of the modern era and it is estimated that there are more than 30 million infected individuals worldwide. Although the major cause is still unclear, patients infected with human immunodeficiency virus are at higher risk of cardiovascular diseases by 60% compared to general population. Material and Methods. This study included 111 male patients infected with human immunodeficiency virus treated at the Clinic of Infectious Diseases, Novi Sad, Serbia from January 2008 to December 2018. Five cardiovascular risk scores were used: Data Collection on Adverse Events of Anti-human immunodeficiency virus Drugs, Framingham 10-year Heart Score, Framingham 5-year Heart Score, prediction algorithm for cardiovascular disease and atherosclerotic cardiovascular disease risk estimator, at the beginning of the treatment, whereas cardiovascular events were recorded during the following 10 years. Results. Data Collection on Adverse Events of Anti-human immunodeficiency virus Drugs, Framingham 10-year Heart Score, Framingham 5-year Heart Score, and prediction algorithm for cardiovascular disease are tools that can identify individuals infected with human immunodeficiency virus at cardiovascular risk with statistical significance. The prediction algorithm for cardiovascular disease provides superior risk estimation compared to other scores. The atherosclerotic cardiovascular disease risk estimator did not show to be a marker of cardiovascular risk prediction among this population of patients. Conclusion. The above mentioned cardiovascular risk prediction algorithms, developed for general population, and Data Collection on Adverse Events of Anti-human immunodeficiency virus Drugs score, specific for population infected with human immunodeficiency virus, allow accurate cardiovascular risk estimation. Until the development of more specific algorithms, these scores are adequate tools for identification of patients at risk, providing prevention measures and treatment of cardiovascular disease. Key words: HIV Infections; Vulnerable Populations; Cardiovascular Diseases; Risk Assessment; Algorithms; ROC Curve; Sensitivity and Specificity; Correlation of Data

Zaključak

Uvod. Infekcija virusom humane immunodeficijencije je bolest modernog doba koja obuhvata više od 30 miliona inficiranih u svetu. Iako je razlog još uvakve nejasan, učestalost kardiovaskularnih bolesti među ovom populacijom je veća za 60% u odnosu na opštu populaciju. Materiaj i metode. Ova studija je uključila 111 muškaraca inficiranih virusom humane immunodeficijencije, lećenih na Klinici za infektni ostalbolesti U Hänskog centaru Vojvodine, od januara 2008. do decembra 2018. godine. Pet skorova za predviđanje kardiovaskularnog rizika: prikupljanje podataka o štetnim efektima lekova protiv virusa humane immunodeficijencije, desetogodišnji rizik za razvoj kardiovaskularnih bolesti, petogodišnji rizik za razvoj kardiovaskularnih bolesti, treća verzija algoritma za procenu rizika za razvoj kardiovaskularnih bolesti i procena rizika za razvoj aterosklerotskih kardiovaskularnih bolesti, treća verzija algoritma za procenu rizika za razvoj kardiovaskularnih bolesti i predviđanjem kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije, treća verzija algoritma za predviđanje kardiovaskularnog rizika kod muškaraca inficiranih virusom humane immunodeficijencije.

Ključne reči: HIV infekcije; ranjive populacije; kardiovaskularna oboljenja; procena rizika; algoritam; ROC kriva; senzitivnost i specifičnost; korelacije
Introduction

Human immunodeficiency virus (HIV) infection is a disease of the modern age and according to some estimates there are more than 30 million infected individuals worldwide. Although prolonged life expectancy is mostly due to antiretroviral therapy, the virus or antiretroviral therapy can lead to higher percentage of chronic diseases or comorbidities in this population, especially cardiovascular diseases CVDs [1].

Studies have shown that the risk of CVDs is by 61% higher in HIV-infected individuals, although the major cause is still unclear [2]. The underlying pathogenesis is a complex combination of traditional risk factors, viral infection and antiretroviral therapy [3].

While there is a clear contribution of traditional risk factors and their high prevalence in people living with HIV, the infection itself causes chronic inflammations and metabolic disturbances caused by antiretroviral therapy that should not be underestimated [4].

There is no doubt that adequate cardiovascular risk calculation may contribute to better management and prevention of morbidity and mortality among this population, but clinicians are still searching for the most suitable risk score [5].

The Framingham heart score (FHS) is widely used to estimate the risk of CVDs in general population and includes general risk factors such as gender, age, systolic blood pressure (SBP) and antihypertensive treatment, high density lipoprotein (HDL), total cholesterol, and the smoking status [6, 7]. Although FHS is recommended in HIV population, there is a dispute among studies, with some pointing to underestimation of cardiovascular risk using this scoring system [5, 7].

American society of cardiology and American heart association (ASC/AHA) developed an atherosclerotic cardiovascular disease (ASCVD) risk estimator which determines 10-year risk of CVD and stroke. It was created for general population aged 40 – 79 years, and includes the following variables: age, gender, race, total and HDL cholesterol, systolic and diastolic blood pressure, antihypertensive therapy, diabetes, and smoking status [8]. Some cohorts have shown that it underestimates the CVD risk, among HIV-infected individuals compared to FHS [9].

The Data Collection on Adverse Events of Anti-HIV Drugs (DAAD) CVD risk score is the only one developed for cardiovascular risk stratification in this specific population and besides traditional risk factors also includes variables such as T-helper (CD4) cell count and antiretroviral therapy exposure [9].

The prediction algorithm for cardiovascular disease (QRISK) score was first established in 2007 in England, and since then it has been updated every year [10]. The QRISK score 3 is the latest version and includes both traditional risk factors (age, sex, ethnicity, cholesterol values, systolic blood pressure and antihypertensive treatment, smoking, diabetes, angina in a first-degree relative) and plenty of variables which are not included in other risk scores, such as atrial fibrillation, chronic kidney disease (stage 3, 4, or 5), migraine, corticosteroid therapy, systemic lupus erythematosus (SLE), atypical antipsychotics, severe mental illness, and erectile dysfunction in men [11]. The estimation of CVD risk by QRISK score has been poorly investigated in HIV-infected individuals [12].

Considering the importance of preventive measures, and adequate screening for those at risk for CVD, the aim of this study was to assess which scoring system is the most accurate for cardiovascular risk evaluation in HIV-infected individuals.

Material and Methods

This retrospective study included 111 HIV-infected male patients treated at the Clinic of Infectious Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia in the period from January 2008 to December 2018. Data were collected from hospital database, using parameters gathered on the time of setting the HIV infection diagnosis in 2008, and medical records on the onset of cardiovascular events (myocardial infarction, stroke or death caused by CVD).

Five cardiovascular risk scores were calculated at the beginning of the treatment, using online available certified calculators: FHS 5-year risk, FHS 10-year risk (https://chip.dk/Tools-Standards/ Clinical-risk-scores), ASCVD score (http://www.cvriskcalculator.com/), DAAD score (https://chip.

| Score/Skor | FHS 10 | QRISK3 | FHS 5 | DAAD | ASCVD |
|------------|--------|--------|-------|-------|-------|
| Number of patients included/Broj uključenih pacijenata | 75     | 108    | 75    | 106   | 39    |

Legend/Legenda: FHS 10 – Framingham heart score/desetogodišnji rizik za razvoj kardiovaskularnih bolesti, FHS5 – Framingham heart score/petogodišnji rizik za razvoj kardiovaskularnih bolesti, QRISK3 – Prediction algorithm for cardiovascular disease 3/treća verzija algoritma za procenu rizika za razvoj kardiovaskularnih bolesti, DAAD – Data Collection on Adverse Effects of Anti-HIV Drugs Study/Prikupljanje podataka o štetnim efektima lekova protiv virusa humane imunodeficiencije, ASCVD – Atherosclerotic Cardiovascular Disease risk estimator/Procena rizika za razvoj aterosklerotskih kardiovaskularnih bolesti
Three patients with missing data were excluded from the study. FHS 5 and FHS 10 cardiovascular risk estimation included patients who were more than 30 years old. ASCVD included patients over 40 years of age at the beginning of the treatment. QRISK 3 was calculated for 108 patients. All statistical analyses were performed using SPSS version 21.

The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value of each score for the prediction of CVDs. The area under the curve (AUC), and 95% confidential interval, sensitivity, and specificity were reported for the whole

Table 2. Differences between FHS 10 risk categories

| FHS 10 | Cardiovascular events/Kardiovaskularni incidenti |
|--------|--------------------------------------------------|
|        | No/Ne | Yes/Da |
| N/Broj | Row/Red N % | N | Row/Red N % |
| Risk level | Kategorija rizika |
| Low/Nizak | 36 | 94.7% | 2 | 5.3% |
| Medium/Srednji | 18 | 78.3% | 5 | 21.7% |
| High/Visok | 7 | 50% | 7 | 50% |

Legend/Legenda: FHS 10 – Framingham heart score/Desetogodišnji rizik za razvoj kardiovaskularnih bolesti

Table 3. Sensitivity and specificity of each score

| Score/Skor | FHS 10 | FHS 5 | QRISK 3 | DAAD |
|------------|--------|-------|---------|------|
| AUC (95%CI) | 0.83 | (0.71-0.94) | 0.77 | (0.62-0.91) | 0.92 | (0.87-0.97) | 0.77 | (0.65-0.92) |
| Sensitivity/Senzitivnost % | 81.3 | 73.3 | 93.8 | 80 |
| Specificity/Specifičnost % | 75 | 76.3 | 83.3 | 71.3 |

Legend/Legenda: FHS 10 – Framingham heart score/Desetogodišnji rizik za razvoj kardiovaskularnih bolesti; FHS5 – Framingham heart score/petogodišnji rizik za razvoj kardiovaskularnih bolesti; QRISK3 – Prediction algorithm for cardiovascular disease 3/treća verzija algoritma za procenu rizika za razvoj kardiovaskularnih bolesti; DAAD – Data Collection on Adverse Effects of Anti-human immunodeficiency virus Drugs Study/Prikupljanje podataka o štetnim efektima lekova protiv virusa humane imunodefijicijencije, AUC – Area under the curve/Površina ispod krive

Table 4. Correlation coefficient among scores

| Score/Skor | ASCVD | QRISK3 | FHS 10 | FHS 5 | DAAD |
|------------|-------|--------|--------|-------|------|
| Spearman’s Rho | Correlation Coefficient/Koeficijent korelacije | 1 | .774** | .696** | .828** | .739** |
| ASCVD Sig. (2-tailed)/Znacajnost (2-zavisna uzorka) | . | 0 | 0 | 0 | 0 |
| N/Broj | 39 | 39 | 39 | 38 | 38 |
| QRISK3 Sig. (2-tailed)/Znacajnost (2-zavisna uzorka) | .774** | 1 | .901** | .919** | .892** |
| N/Broj | 39 | 112 | 112 | 74 | 106 |
| FHS 10 Sig. (2-tailed)/Znacajnost (2-zavisna uzorka) | .696** | .901** | 1 | .964** | .892** |
| N/Broj | 39 | 112 | 112 | 74 | 106 |
| FHS 5 Sig. (2-tailed)/Znacajnost (2-zavisna uzorka) | .828** | .919** | .964** | 1 | .893** |
| N/Broj | 38 | 74 | 74 | 74 | 74 |
| DAAD Sig. (2-tailed)/Znacajnost (2-zavisna uzorka) | .739** | .892** | .892** | .893** | 1 |
| N/Broj | 38 | 106 | 106 | 74 | 106 |

Legend/Legenda: FHS 10 – Framingham heart score/desetogodišnji rizik za razvoj kardiovaskularnih bolesti; FHS 5 – Frameingham heart score/petogodišnji rizik za razvoj kardiovaskularnih bolesti, QRISK3 – Prediction algorithm for cardiovascular disease 3/treća verzija algoritma za procenu rizika za razvoj kardiovaskularnih bolesti, DAAD – Data Collection on Adverse Effects of Anti-human immunodeficiency virus Drugs Study/Prikupljanje podataka o štetnim efektima lekova protiv virusa humane imunodefijicijencije, ASCVD – Atherosclerotic Cardiovascular Disease risk estimator/Procena rizika za razvoj aterosklerotskih kardiovaskularnih bolesti
sample. The ROC curves were interpreted as the probability that the estimated interval values can adequately discriminate patients with cardiovascular risk and without it (where 0.5 is chance discrimination and 1.0 is perfect discrimination). The correlation coefficient was calculated between the tests.

Results

A total of 111 HIV-positive male patients were included in this study, with an average age of 37.48 ± 11.67 years, at the time when HIV infection was diagnosed. All the scores except ASCVD could estimate the cardiovascular risk among HIV-infected individuals with statistical significance. All patients included in calculation are presented in Table 1. Cut off values for each score were calculated using ROC curve.

The prediction algorithm for cardiovascular disease (QRISK3) score of 4.35 or higher identified cardiovascular risk in HIV-infected individuals with sensitivity of 93.8%, specificity of 83.3% (AUC 0.92, 95% CI, 0.87 – 0.97, p < 0.000).

In risk assessment, the value of 10 or higher calculated using FHS 10-year showed a sensitivity of 81.3% and specificity of 75% (AUC 0.83, 95% CI, 0.71 – 0.94, p < 0.000).

There was a difference in frequency of cardiovascular events among FHS 10-year risk categories ($\chi^2=13,693; p=0,001$). Patients with high risk scores, compared to low category risk scores, showed higher incidence of cardiovascular events (7 (50.0%) vs. 2 (5.3%); p < 0.001) (Table 2). Framingham 5-year heart score of 2.75 (AUC 0.77, 95% CI, 0.62 - 0.91, p < 0.001) and DAAD of 2.32 (AUC 0.77, 95% CI, 0.65 - 0.92, p < 0.000) showed a sensitivity of 73.3%, 80% and specificity of 76.3%, 71.3% in cardiovascular risk assessment, respectively (Table 3). All tests showed high correlation coefficients between each other (Table 4).

Discussion

This study investigated 4 scoring algorithms developed for general population and I developed specifically for HIV population to assess the cardiovascular risk.

In our country, CVDs are number one cause of death since 1980s, and in 2007 the CVD-related deaths in all-cause mortality accounted for 56% [13].

The trend of rising CVD mortality in HIV-infected individuals is growing in importance [14]. In 2010, 19% of HIV-infected individuals had at least one CVD [15, 16].

While there are many data showing HIV infection itself seems to be one of the risk factors for CVD, there are no such algorithms to include HIV infection as a parameter [17, 18].

Our study has shown that FHS 5 and FHS 10-year scores, DAAD score and QRISK3 score are reasonable to use for CVD risk estimation among HIV-infected individuals.

However, ASCVD score did not predict the risk accurately, which was also reported in some previous studies [5]. In our study this can be explained by a small sample size, while only patients who were 40 years or older were included in the score calculation.

In our study, QRISK3 showed the highest accuracy in identifying subjects at risk of CVDs, with the highest sensitivity and specificity compared to other scores. The score itself was developed for risk stratification of the population of the United Kingdom, while there are no clear limits of using it for CVD risk estimation in other populations [11]. The role of this algorithm and its accuracy for HIV-infected individuals has not been investigated in previous studies. It will be interesting to check the sensitivity of this score in a larger group of HIV patients.

A recent study conducted in the Netherlands found that FHS risk score is acceptable in HIV-infected individuals, as was confirmed by our results. Both FHS scores, which estimate the 5 and 10-year CVD risks, were good at risk stratification in our study [19].

Data Collection on Adverse Events of Anti-HIV Drugs is the only scoring algorithm developed for HIV patients, and includes antiretroviral therapy exposure and duration of the treatment. The role of this score in CVD risk assessment is still unclear [5, 19, 20]. Its property to identify subjects at risk is inferior compared to QRISK3 score, but also statistically significant. This implicates that in our study the sample size or other parameters, rather than antiretroviral therapy exposure or duration of the treatment, contribute to CVD risk. However, we cannot underestimate the role of some drugs, for example abacavir and duration of exposure, as well as the duration of HIV infection prior to the treatment [21, 22].

All scores showed high correlation coefficient between each other which shows that one score calculation is enough to determine the cardiovascular risk.

The main advantage of this study is that it estimated the cardiovascular risk among HIV-infected subjects in Vojvodina for the first time, but the sample size is relatively small.

Conclusion

This study showed that four risk scores (Data Collection on Adverse Events of Anti-human immunodeficiency virus Drugs, Framingham 10-year Heart Score, Framingham 5-year Heart Score, prediction algorithm for cardiovascular disease) are reasonable to use for cardiovascular risk stratification among individuals infected with human immunodeficiency virus, while the atherosclerotic cardiovascular disease risk estimator is not suitable for this specific population. The prediction algorithm for cardiovascular disease 3 score showed the best results in identification of subjects at risk, with high sensitivity and specificity, while its usage among subjects infected with human immunodeficiency virus...
ciency virus has not been previously investigated. This opens a topic for future investigations. Although cardiovascular risk stratification among individuals infected with human immunodeficiency virus remains challenging, studies including new parameters in scoring algorithms may provide additional insights. Until then, the usage of algorithms developed for general population is useful for identification of patients at risk.

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