Elchin Huseynov Mammad oglu. Prognosis of complications of acute brucellosis from hepatobiliary and cardiovascular systems. Journal of Education, Health and Sport. 2019;9(2):607-614. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3520968
http://ojs.ukw.edu.pl/index.php/johs/article/view/7607

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

Received: 05.02.2019. Revised: 11.01.2019. Accepted: 28.02.2019.

Prognosis of complications of acute brucellosis from hepatobiliary and cardiovascular systems

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Abstract

Brucellosis is a worldwide spread bacterial zoonosis, causing the globality of the problem. Brucellosis is a systemic disease with a wide range of clinical features that can cause pathological changes in any organ of the human body. The purpose of our study was to predict the onset of acute brucellosis depending on the activity of the inflammatory process and the development of complications. In order to reproduce the process of occurrence of both complications with associated risks, we applied a bivariate probit model. The risk of cardiovascular complications in patients with acute brucellosis of TLR-4 A/G genotype was found to be reduced by 94.67% in comparison with G/G carriers and by 56.39% among A/A genotype carriers compared to G/G genotype carriers. The risk of complications of the hepatobiliary system among carriers of the genotype G/C of the IL-6 gene compared to carriers of the genotype C/C is reduced by 10.75%.

Keywords: acute brucellosis; prognosis; complications.

Relevance: Brucellosis is a common bacterial zoonosis. More than 500,000 new cases of brucellosis are reported annually in the world, which determines the global nature of this

problem. Thus, in some countries, the incidence of brucellosis is 10 cases per 100,000 populations [1]. The disease is endemic to most Mediterranean countries, the Middle East, subcontinental India, parts of Mexico, Central and South America [2]. Of the sixty-two countries identified as having the highest incidence of brucellosis, Azerbaijan is now in thirteenth place with an estimated annual incidence as of year 2000 - more than 50 cases per million [3].

Brucellosis is a systemic disease with a wide range of clinical features that can cause pathological changes in any organ of the human body [4]. The liver, as the largest organ of the reticuloendothelial system, is being affected in virtually all brucellosis patients. The involvement of the liver in the pathological process may be accompanied by increased levels of transaminases, hepatosplenomegaly, rarely the development of acute hepatitis. Abscesses may occur even less frequently. Thus, according to the scientific data, liver injury in brucellosis occurs in one third of patients, namely, ranges from 3% to 40% in different populations [5].

A number of mediators of the inflammatory process, such as leukotrienes, cytokines, interleukins, and others, are direct damaging factors in relation to the cardiovascular system, namely the myocardium. Their activation is associated with the direct negative effect on cardiomyocytes and the indirect effect through the disruption of microcirculation, activation of lipid peroxidation, induction of apoptosis, stimulation of fibrosis [6]. However, changes in the cardiovascular system at the organ level, especially in acute brucellosis, have not been sufficiently investigated and are quite rare. Thus, according to various data, complications in the cardiovascular system in patients with brucellosis occur in less than 2% of patients. Most often, these complications occur in the form of endocarditis [7, 8]. Unlike endocarditis, which is the most common complication, acute pericarditis and myocarditis without endocardial involvement are met rarer, even in countries with high prevalence of the disease.

Therefore, the **purpose of our study** was to predict the onset of acute brucellosis, depending on the activity of the inflammatory process and the development of complications.

Materials and methods of research:

Design of the prognosis model: effective signs are the presence / absence of complications of acute brucellosis from a) hepatobiliary system and b) cardiovascular system. Traditionally, logistic or probit models are traditionally used to predict each complication. However, the situation is significantly complicated by the link between the risks of both complications occurrence. The presence of such a connection is justified by the onset of acute brucellosis. In order to be able to reproduce the process of occurrence of both complications

with associated risks, we applied the ***bivariate probit model***, which describes the possibility of risk sharing through a common covariance matrix of both consequences. The mechanism of generation of two consequences is thus combined into one process through two-dimensional normal distribution. To this end, the risks of complications of acute brucellosis from a) the hepatobiliary system and b) the cardiovascular system are represented by the latent variables W [, 1] and W [, 2], respectively, which according to the probit model have a normal distribution. In the program code script, the implementation is based on the augmented data approach. Among the predictors of complications of acute brucellosis from the hepatobiliary and cardiovascular system are both the individual characteristics of the patient and the course of brucellosis, some of which are typological, and are also continuous.

Organization of the data: the data contained information about the patient in the form of two productive variables: presence (1-present, 0-absent) complications from the hepatobiliary system (Hepar), complications from the cardiovascular system (Card), patient identification code (variable ID with values from 1 to 120). Predictors were individual patient characteristics (factors), namely: age (Age), gender (Gender, 1-male, 0-female), IL-4 polymorphisms (PolyIL4, T|T=0, C|T=1, C|C=2) та IL-6 (PolyIL6, C|C=0, G|C=1, G|G=2), TLR-2 (PolyTLR2, Gln|Gln=0, Arg|Gln=1, Arg|Arg=2) and TLR-4 (PolyTLR4, G|G=0, A|G=1, A|A=2). Important indicators of acute brucellosis were also used as predictors (with variable names and normal limits):

1. ALT max 40
2. AST max 40
3. Hemoglobin (Hb) min 120
4. Leukocytes (L) max 10 (*10^9)
5. Platelets (Tromb) min 180
6. ESR min 10
7. C-reactive protein (C) max 9
8. IL4 max 7
9. IL6 max 10
10. TLR-2 max 3500
11. TLR-4 max 300

The indicators of brucellosis progress have been transformed into relative indicators, namely standardized indices (Index) using the formula:

$$Index = \frac{Index_1 - lim}{\lim \square},$$

where *Index1* - indicators value before treatment,

lim - corresponding limit of norm (upper at the excess and lower at the lower state of the indicators due to the brucellosis).

Thus, the formed indexes indicate the initial severity of acute brucellosis - higher modulus values indicate a more severe condition. Another advantage of transformation is the comparability of indicators due to standardization.

Multiple Gradation Effect Specifications: These include the effects of IL-4, IL-6 polymorphisms, and TLR-2 and TLR-4 polymorphisms.

Testing the predictive ability of the model.

We have used the most powerful approach with poster-cross-validation of the leave-one-out type to test the model's predictive ability. The posterior density distribution of the model parameters $p(\theta|y)$ is used as a proposal distribution to approximate the posterior parameter distribution with the excluded indexed patient $p(\theta|y\backslash i)$.

At each iteration of the MCMC, the $CV^{(t)}$ is estimated. With perfect predictive power of the model, the averaged MCMC values of CV on the simulated external sample (CV [2,1..2] in the script) coincides with the averaged MCMC value of CV on the observed sample of patients (CV [1,1..2]). The statistics itself is designated as PPC, and its values around 0.5 indicate perfect predictive power of the model. The part of the script code that calculates the PPC has comment ## Posterior predictive check with coefficients of variation (CV).

Implementation and software: The analytical software module is written in WinBUGS, an acronym for Bayesian inference using Gibbs (software). The model parameters were calculated in WinBUGS version 1.4. Preliminary data preparation and convergence studies in Markov chains were performed in the CODA package of mathematical analytical system R version 3.1.0. All of the graphic images are also created in R (GRAPHICS package).

Results and Discussion

The strength of the MCMC methodology is the possibility of distribution of parameter estimates based on a posteriori distributions, which cannot be performed within the framework of classical statistics estimators. This is one of the significant advantages that has made data analysis by MSMS algorithms this popular. The values of 5% (0.05), 50% (median as the most typical value) and 95% (0.95) of the percentiles of the posterior distributions of parameter estimates are classically allocated. Markov chains had good convergence. Centiles of a posterior distributions of estimates of the parameters of the model of prognosis of complications of acute brucellosis from the hepatobiliary and cardiovascular system are shown in the table in Fig. 1.

First of all, it follows that the correlation between the risks of two complications (rho = 0,163) is not reliable.

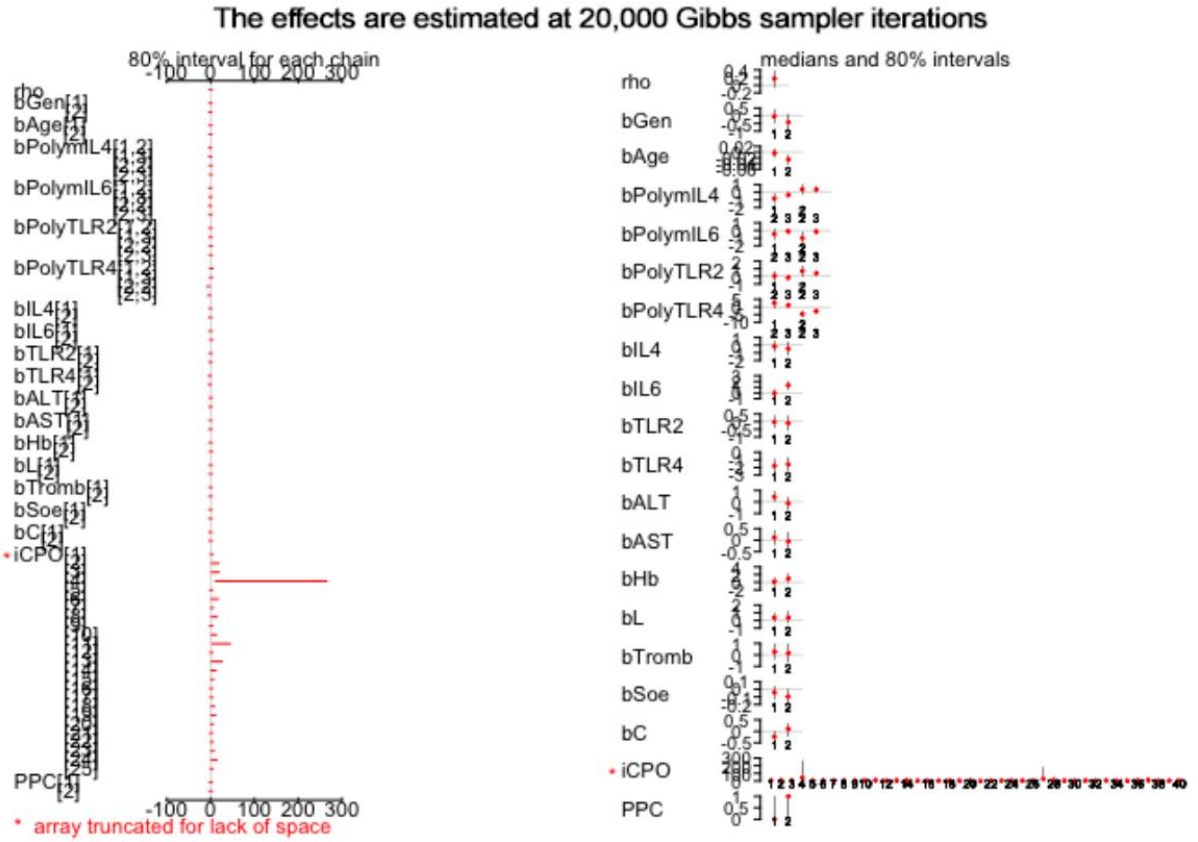

Fig.1 - A posteriori distributions of the MCMC parameters of the bivariate probit model

The certainty of the most important predictors of modeling results of complications of acute brucellosis of the hepatobiliary and cardiovascular system follows from the centiles of posterior distributions of parameter estimations:

●IL6 (effect bIL6 [2]), since 0 is within 95% of the interval, namely [0,286; 2,353]. A positive sign of the effect indicates that larger deviations of IL-6 from the upper limit of the norm provoke a higher risk of complications from the cardiovascular system.

●Significant negative values of bPolyTLR4 [2,2] and bPolyTLR4 [2,3] indicate significantly lower risks of cardiovascular complications with TLR4 polymorphisms A|G vs. G|G and A|A vs. G|G

●Significant negative values bPolymIL6 [1,2], bPolymIL6 [1,3], bPolymIL6 [2,2], and bPolymIL6 [2,3] indicate significantly lower risks of complications from both the hepatobiliary and cardiovascular systems for IL6 polymorphisms G|C against C|C and G|G against C|C.

● Age (bAge effect [2]). The negative effect indicates a higher risk of complications from the cardiovascular system in older patients.

According to the results of calculations we get LP1 = 0,21, LP2 = 0,179.

Quantitative evaluation of the effects of TLR4 polymorphism.

Determining the reduction of the risk of complications on the part of the cardiovascular system with more favorable TLR4 A|G polymorphism versus less favorable G|G. The coefficient of bPolyTLR4 [2,2] (its average posterior distribution) is -4.6, ie $-4.6\phi\ (LP_2)$ = -4.6 * 0.2058 = -0.9467, ie the risk is reduced by 94.67%.

Thus, the risk of cardiovascular complications with TLR4 A|G versus G|G polymorphisms is reduced by 94.67%.

Determining the reduction of the risk of complications from the cardiovascular system with a more favorable TLR4 A|A polymorphism versus a less favorable G|G. The coefficient of bPolyTLR4 [2,3] (its average posterior distribution) is -2.741, ie $-2.74\phi\ (LP_2)$ = -2.74 * 0.2058 = -0.563892, ie the risk is reduced by 56.39%.

Thus, the risk of cardiovascular complications with TLR4 A | A vs. G | G polymorphisms is reduced by 56.39%.

Quantitative evaluation of the effects of IL6 polymorphism.

Similarly, determining the reduction of the risk of complications from the hepatobiliary system with a more favorable polymorphism of IL6 G|C versus C|C, since the regression coefficient bPolymIL6 [1,2] = -0,500 was negative and significant. We calculate $-0.5\phi\ (LP_1)$= -0.5 * 0.215 = -0.1075, that is, the risk of complications from the hepatobiliary system with a more favorable polymorphism IL6 G|C versus C|C is reduced by 10.75%.

Determining the reduction of the risk of complications from the hepatobiliary system with a more favorable polymorphism of IL6 G|G versus C|C, since the regression coefficient bPolymIL6 [1,3] = -0,115 was negative and significant. We calculate $-0.115\phi\ (LP_1)$= -0.115 * 0.215 = -0.0247, that is, the risk of complications from the hepatobiliary system with a more favorable IL6 G|G versus C|C polymorphism decreases by 2.47%.

Similarly, determining the reduction of the risk of complications from the cardiovascular system in more favorable polymorphism IL6 G|C vs. C|C, since the regression coefficient bPolymIL6 [2,2] = -0,998 was negative and significant. We calculate $-0.998\phi\ (LP_2)$= -0.998 * 0.2058 = -0.2054, that is, the risk of complications from the cardiovascular system with a more favorable IL6 G|C versus C|C polymorphism is reduced by 20.54%.

Analyzing the reduction of the risk of complications from the cardiovascular system with a more favorable polymorphism of IL6 G|G versus C|C, since the regression coefficient bPolymIL6 [2,3] = -0,142 was negative and was significant. Calculating $-0.142\phi\ (LP_2)$= -0.142 * 0.2058 = -0.0292, ie the risk of complications from the cardiovascular system with a more favorable IL6 G|G versus C|C polymorphism is reduced by 2.92%.

Quantitative assessment of the effect of exceeding the upper limit of IL6.

Determining the increased risk of complications from the cardiovascular system with an increase in IL6 values by 100% above the upper limit of normal. The regression coefficient bIL6 [2] = 1.327 had a positive value and was significant. We calculate $1.327\phi\ (LP_2)$= 1.327 * 0.2058 = 0.2731, that is, the risk of complications from the cardiovascular system when increasing IL-6 values by 100% above the upper limit of normal increases by 27.31%.

Thus, brucellosis remains a significant health problem for endemic countries. Given the polymorphism of symptoms, the multisystem of this disease, there are difficulties in early diagnosis of the disease and verification of complications [9]. Along with the most common internal organs, it is necessary to be alert to the possible damage to the hepatobiliary system in patients with brucellosis. The incidence of liver damage varies greatly according to various researchers. Thus, the incidence of hepatomegaly ranged from 4.3% to 22.4% [10, 11].

Patients with acute brucellosis require a more thorough study of the condition of the cardiovascular system with the obligatory use of instrumental methods of examination in order to detect early signs of its lesion, timely involvement of appropriate therapeutic measures, as well as to study genetically determined developmental development of patients with brucellosis [12, 13].

Conclusions:

1. The risk of cardiovascular complications in patients with acute brucellosis of TLR4 genotype A/G gene carriers is reduced by 94.67% compared to carriers of the genotype G/G and by 56.39% among A/A genotype carriers compared to G/G genotype carriers.
2. The risk of complications from the cardiovascular system in the genotype G/C of the IL-6 gene when compared with the genotype C/C decreases by 20.54% and increases by 27.31% when increasing the content of IL-6 in the serum by 100% above the upper limit of the norm values.
3. The risk of complications from the hepatobiliary system among carriers of the G/C genotype of the IL-6 gene compared to carriers of the C/C genotype is reduced by 10.75%

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