Modeling Dependence Between Disability Status and Health Service Costs of Patients with Rheumatoid Arthritis in Hungary

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BACKGROUND AND KEYWORDS

RA DISEASE: Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes pain, stiffness and also limited motion and function of joints.

HAQ: The Health Assessment Questionnaire (HAQ) is a self-report questionnaire measuring disability level of patients with RA by the HAQ-index on a scale from 0 (no difficulty) to 3 (unable to do).

OBJECTIVE: The main objective of this study is to estimate the impact of the level of functional status and disability on health service cost related to RA disease in Hungary.

DEPENDENCE: Although it is straightforward to think that higher disability implies higher costs the nature of the relationship is unclear.

COPULA: Nowadays there are more and more recent copula models aimed at describing the behavior of multivariate data sets.

JOINT DISTRIBUTION: Instead of fitting only trend lines for the expected value of the cost the entire bivariate distribution has been modeled.

STATISTICAL METHODS

LINEAR MODELS are not suitable for non-linear relationships and even GLM works only for limited distribution families.

COPULA: Copulas [Nelsen, 2006] are simple but yet powerful tools for modeling, which ensure the separation of marginal modeling and dependence structure.

$$H(x,y) = \Pr\{(X,Y) \le (x,y)\} = C(F(X),G(Y))$$

where *F* and *G* are the marginal distribution functions and *C* is the copula distribution function.

MODELS: There are several parametric families available, for elliptical families see *Figure 1.* below:

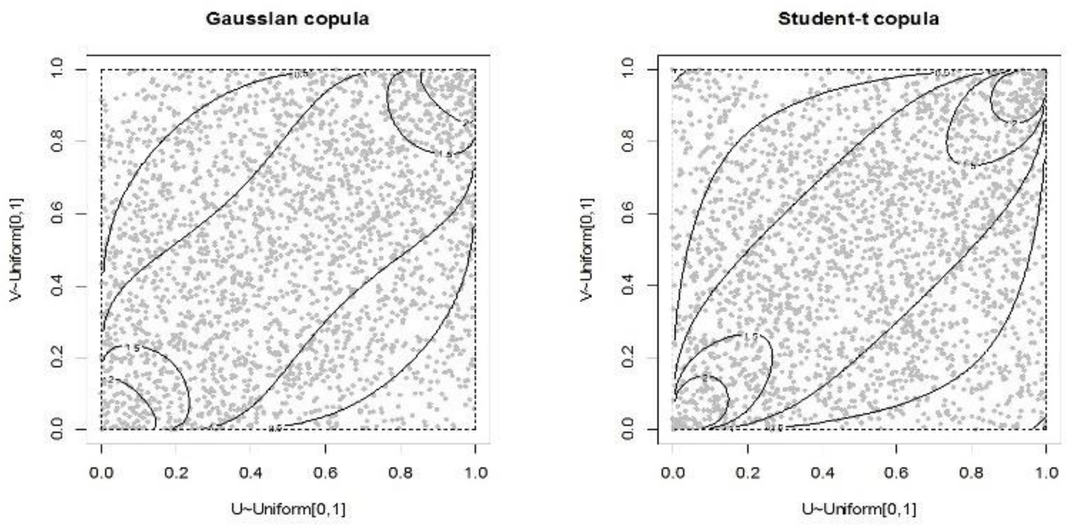

Figure 1. Density curves of Gaussian (θ=0,5 on the left) and Student-t (θ=0,5 / df.=4 on the right) copulas

PROS: Non-linear structures are applicable / No restrictions on marginal distributions

CONS: Testing the goodness-of-fit (GOF) and handling covariates are complicated.

GOF: The performance of the different model assumptions can be compared by GOF procedures based on the $K(t) = \Pr\{C(u,v)) \le t\}$ function.

MIXTURE: In practical applications it is possible that the marginal distributions are not continuous, in such cases mixture models can be used. Similarly to zero-inflated models there is often positive probability observed at zero, these can be estimated easily by relative frequencies (p_{xy}, p_x, p_y) as in *Table 1.*

$$H(x,y) = p_{xy} + p_x \Pr\{X \le x\} + p_y \Pr\{Y \le y\} + (1 - p_{xy} - p_x - p_y) \Pr\{(X,Y) \le (x,y)\}$$

SOFTWARE: Pseudo-maximum likelihood estimates of copula parameters are available using the 'copula' package [Kojadinovic and Yan, 2014] of the R statistical programming language.

OUTPUT: After the model estimation any conditional expectations (see *Table 2.*) or conditional probabilites (see *Figure 3.*) become obtainable.

EXTENSIONS

COVARIATES: Covariates can be included as additional model parameters e.g. gender/age/ treatment type etc.

MORE FAMILIES: Different parametric assumptions can be applied, e.g. asymptotic dependence/independence or inbetween.

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DATABASE

AC: HAQ-indices of RA patients were collected in the Arthritis Center (AC) of Buda Hospital of Hospitaller Brothers of St. John from 1st January 2001 to 31st March 2014.

NHIFA: RA patients were identified in the database of National Health Insurance Fund Administration (NHIFA) and further parameters as e.g. relevant treatments and health service costs (in- and outpatient) were collected from 1st January 2005 to 31st July 2013.

PERMISSION: 26513-3/2013/EKU (329/2013.) by Scientific and Research Ethics Committee of the Medical Research Council

MERGE: After merging AC (497 patients) and NHIFA (43 836 patients) database the 2-dimensional patterns of the HAQ-index measurements versus costs (sum of relevant costs in the following year) and several covariates became available for bivariate modeling.

STUDY PERIOD: There have been 324 patients with 2115 HAQ-index observations available in the AC-NHIFA merged database from 1st January 2005 to 31st July 2013.

EXCHANGE RATE: HUF-USD currency conversion has been made according to the quarterly average rate of the Central Bank of Hungary (2014 Q2)

FITTED MODEL

INCLUSION CRITERIA: In our example, observations are modeled only after the RA diagnosis.

COST TYPE: Yearly cost of inpatient care started from the date of the HAQ index measurement.

TECHNICAL INFO: In order to decrease the number of overlapping time periods for patients having frequent HAQ measurement there is gap rule of 180 days for consecutive observations applied.

ESTIMATES: The observed rates of the mixture model can be found in Table 1 below:

Mixture Rates	p_{xy} (%)	p_x (%)	p_y (%)	Positive quadrant (%)
Rel. frequency	5,4	53,8	0,2	40,6

Table 1. 40,6% of the observation points are in the positive quadrant

The empirical marginal distributions (black lines) and their parametric versions (red lines) assuming normal distribution for HAQ (*μ=1,4* and *σ=0,7)* and log-normal distribution for the inpatient care cost *(μ=6,4* and *σ=0,6*) are presented in the upper panels of *Figure 2.* The dependence parameter of the Gaussian copula is *0,17(0,07)* which is significantly greater than zero (p-value<*0.01*).

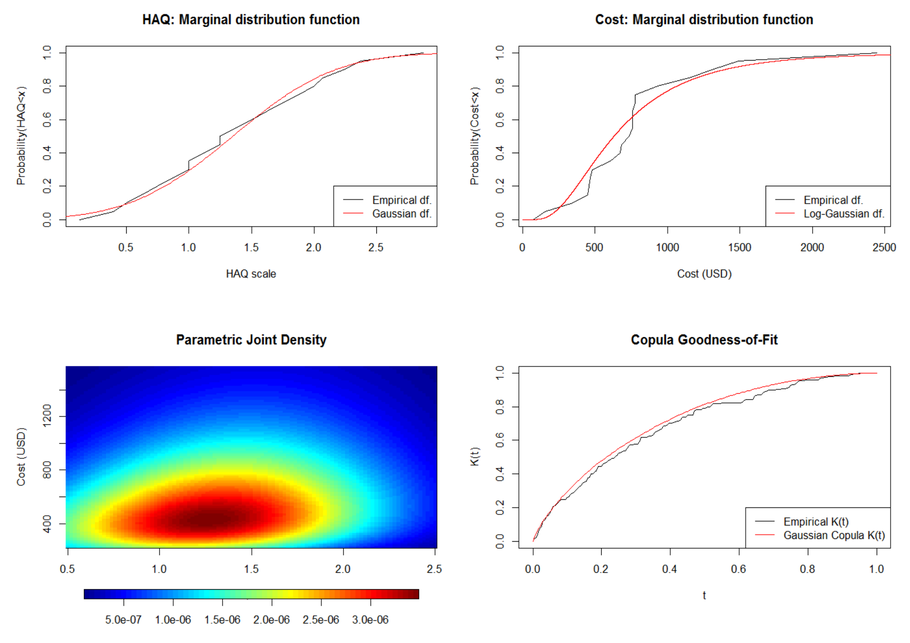

Figure 2. Marginal distribution of HAQ and Cost, Density of the bivariate joint model, Difference between K functions, respectively

SUMMARY

RESULTS: Average costs in out/inpatient care and total cost have been estimated based on the fitted mixture models. The actual values are summarized in *Table 2.* There is positive dependence found in all cases which means that the average cost increases with higher values of HAQ indices.

HAQ-index	Expected Cost of Outpatient Care	Expected Cost of Inpatient Care	Expected Total Cost (excluding Biologics)
Low (0,5)	$74	$646	$10 078
Medium (1,25)	$77	$694	$10 437
High (2,25)	$80	$715	$10 870

Table 2. Expected costs of out/inpatient care and total cost excluding biologics

CONDITIONAL DISTRIBUTIONS: Beyond expectations any conditional distribution can be obtained, see *Figure 3* for illustration.

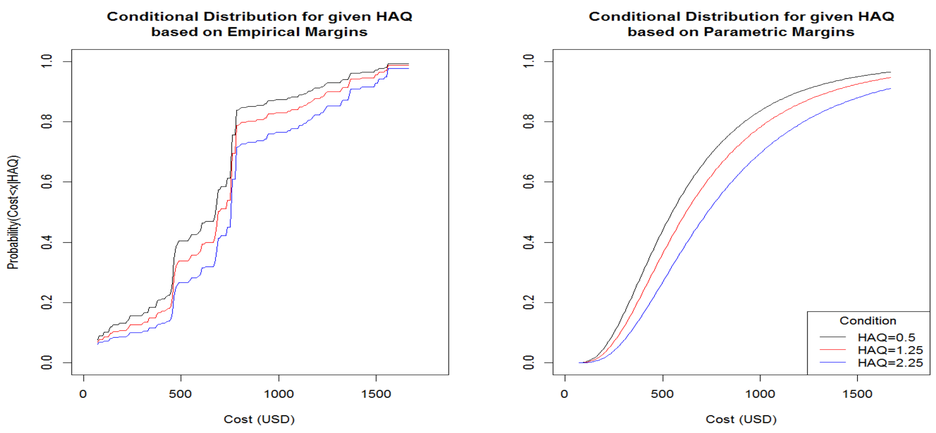

Figure 3. Conditional distribution functions at low/medium/high HAQ values

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