Predictive models for utility from positive and negative syndrome scale clinical questionnaires for Schizophrenia in the United Kingdom, France and Germany – Findings from the European Schizophrenia Cohort (EuroSC)

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Abstract

In cost-utility analyses, the utility values are rarely available and are generally predicted by extrapolating (using a "mapping" function) a known clinical questionnaire. Knowing the relationship between the utility values and patient's variables and covariables (by providing the estimated "mapping" function) allows to predict the utility value from clinical informations for new samples, and will be useful in health-economics studies for cost-utility analysis. These clinical informations are more easily collected than utility value, in a more direct and chipper way.

The clinical symptoms of the schizophrenia are associated to serious alterations of the physical functioning, social functioning, and of the QoL. The impact of the various alterations for each domain on the utility value has not been assessed yet.

The purpose of this article is to provide such a mapping for schizophrenic patients. We determine among the schizophrenic patient's characteristics, what are the variables (clinical, functional, symptoms, Quality of Life -QoL-) and co-variables (age, sex, country) that are predictive factors for the utility value of each patient.

This analysis is conducted and compared in three European countries : France, Germany and United-Kingdom.

Keywords: Schizophrenia, quality of life, positive and negative syndrome scale, mapping.

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1 Introduction

Economic evaluations are designed to compare several alternative therapies in terms of costs and outcomes. They allow decision-makers to consider the value of alternative uses of available resources. Cost-utility analyses are a common type of economic evaluation. The primary outcome of a cost-utility analysis is the incremental cost-effectiveness ratio (ICER), known as the cost per QALY. It is calculated as the difference in the expected cost of two interventions, divided by the difference in the expected QALYs produced by the two interventions. In order to estimate QALYs, appropriate utility values are required.

Schizophrenia affects approximately 1% of the general population, usually before the age of 25, throughout life. There exists a high heterogeneity in manifestation of symptoms: positive symptoms are those that appear to reflect an excess or distortion of normal functions (including hallucinations, delusions, racing thoughts), negative symptoms reflect a diminution or loss of normal functions (including apathy, lack of emotion, poor or missing social functioning) and disorganized symptoms include disorganized thoughts, difficulty concentrating and/or following instructions, difficulty completing tasks and memory problems.

Utility is mainly seen as a multidimensional concept, which measured different aspects of life in a variety of ways. It is a main indicator for better outcomes in patients with schizophrenia as well in different kind of diseases. Since schizophrenic clinical symptoms are associated to serious functioning, social, and quality of life (QoL) alteration, assessing its utility is an important challenge. However, in cost-utility analyses, utility measures are rarely available and they are generally predicted using a "mapping" extrapolation from a clinical questionnaire (and other co-variables). The impact of the various domain alterations on utility measure has not been assessed. Consequently, being able to develop a predictive equation to estimate utility measure based on clinical, functioning and QoL variable would address unmet needs for health economics assessment.

Quality of life has emerged as a key concept in assessing the impact of an illness on people's day-to-day lives. It is one of the key outcome variables in the treatment of schizophrenia (M et al. [2008]). Several studies have investigated independent predictors of QOL in people with schizophrenia. These studies stated that clinical factors such as positive and negative symptoms, depression, and extra-pyramidal symptoms are associated with low QOL (FB et al. [1998], TE et al. [1999], RMG et al. [2000], P et al. [2005], SA et al. [2005]; Bozikas et al., 2006; A et al. [2006], H et al. [2008], K et al. [2008]). In 2010, Mavranezouli [2010] reported that 7 cost-utility analysis were performed. Out of these, none used utility values for schizophrenia generated using the EQ-5D, which is a measure widely used in cost-utility analysis and preferred by NICE.

The objectives of this article are to determine in schizophrenic patients which variables (clinical, functioning, QoL symptoms, compliance etc.) and which co-variables (age, sex, sociodemographic) are predictors of utility measured by EQ-5D and SF-6D. The link between utility measures and subscores of the positive and negative syndrome scale (PANSS) for schizophrenia is investigated. Other co-variables are used: age, sex, depression, compliance, non-compliance, side effects, medication variables, Global Assessment of Functioning, Abnormal Involuntary Movement Scale, Barnes Akathasia Scale, Simpson and Angus Scale. Two predictive models are developed for more flexibility according to the clinical variables available to the practitioners: the predictive equation for utility score will be presented according to various co-variables.

The analysis is conducted and compared in three European countries: France, Germany and the United Kingdom, from the European Schizophrenia Cohort (EuroSC). In the European Schizophrenia Cohort, a naturalistic two-year follow-up study of 1208 patients. Utility is computed based on ED5D using UK social tariff.

The relationships between the variables are modeled using random individual effects panel.

The analysis provides evidence of predictors of utility measure in schizophrenic patients. Although there are small variations between countries, the same variable appears to be the key predictors. The predictive equations allow computing utility measure of schizophrenic patients when only clinical or clinical and functional variable have been measured.

The paper is organized as follows. section 2 presents the data, the instruments, the predictive models, and the statistical model. section 3 presents the results with respect to both the predictive models. section 4 presents the discussion, and finally, concludes.

2 Data and methods

2.1 Design and sample

The EUROSC (European Schizophrenia Cohort) cohort is a European cohort conducted in France, Germany and UK, with a prospective follow-up from 1998 to 2001. 1208 participants were interviewed at 6-monthly intervals for a total of 2 years. The following data were collected: France (N=288), Germany (N=618), et United Kingdom (N=302). It was sponsored by Lundbeck. Its first objective was to identify and describe the types of treatment and

methods of care for people with schizophrenia, and to correlate these with clinical outcomes, states of health, and quality of life.

Information about the use of services during the preceding six month period was collected from patients or patients' key-workers. It covered hospital-based services, day clinic activities, outpatient physician and psychological services, and medications used by the patient. For each service, information was collected on the type of service, the frequency of attendance and type of intervention provided to the patient.

In each country, catchment areas were chosen based on socio-demographic and had styles of service delivery. Nine European centers were considered: two in Britain, four in Germany and three in France. The specific locations were chosen because they are socio-demographically distinct and have different styles of service delivery.

The participants were selected to provide a representative sample of the patients treated in secondary psychiatric services in each catchment area.

Random sampling from these patients was used to generate a representative sample. This project was conducted in accordance with the Declaration of Helsinki and French Good Clinical Practices CNIL [2004], WMA [2008].

A description of the study's rationales and methods is presented by Bebbington et al. [2005].

2.2 Instruments

The data collected included past psychiatric and service history, socio-demographic information and clinical information. The clinical information covered diagnosis, current psychiatric and social state, needs for care and treatment, quality of life, the consumption of medication, side effects, adherence to treatment, pathway through the care system and the consumption of service resources.

EuroQol EQ-5D

The utility measure is computed from the multi-attribute EuroQol EQ-5D questionnaire, using the British scorage formula. The EQ-5D measure consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For more detail, see `http://www.euroqol.org/eq-5d/what-is-eq-5d/eq-5d-nomenclature.html`.

SF-6D

For a comparison purpose, the SF-6D is also evaluated. [1] The SF-36 is the most widely used measure of general health in clinical studies. It generates eight dimension scores and two summary scores for physical and mental health. Such scores provide a good means for judging the effectiveness of health care intervention, but they have only a limited application in economic evaluation because they are not based on preferences.

The SF-6D provides a means for using the SF-36 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D is composed of six multi-level dimensions. Any patient who completes the SF-36 or the SF-12 can be uniquely classified according to the SF-6D. The SF-6D describes 18,000 health states in all.

Positive and negative syndrome scale (PANSS)

PANSS is a comprehensive tool that includes 30 items, necessitating a long interview with the patient (30-40 minutes). Items are assessed based on patient perceptions relating to their experiences in the previous week.

It includes a positive subscore (PANSS_POS) based on the following items: delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness/persecution and hostility ; a negative subscore (PANSS_NEG) based on blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking ; and a general psychopathology subscore (PANSS_PSY) based on somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, un-cooperativeness, unusual thought, content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation, and active social avoidance.

PANSS_POS and PANSS_NEG contain 7 items from 1 (no problem) to 7 (problem). The PANSS_POS and PANSS_NEG scores go from 7 (no problem) to 49 (problem) . PANSS_PSY contains 16 items from 1 (no problem) to 7 (problem). The PANSS_PSY score goes from 16 (no problem) to 112 (problem).

2.3 Predictive models

The aim of the paper is to develop predictive models for utility measures obtained only from clinical questionnaires for Schizophrenia, using "mapping" extrapolation. Two predictive models are developed for more flexibility according to available clinical variables for practitioners.

For that purpose, the link between the utility measures and subscores of the PANSS is investigated. Other co-variables are also used: age (AGE), sex (SEX), anti-psychotic type (AP) that can be typical, atypical, or mixed (containing at least one typical anti-psychotic and one atypical anti-psychotic),

[1] The algorithm for deriving the SF-6D utility from the SF36 subscores is provided in the following web page: `http://www.openhealthmeasures.org/repository/index.html`.

depression (CDSS) [2], Global Assessment of Functioning (GAF) [3], the Clinical Global Impression - Severity scale (CGI_S) [4], the Clinical Global Impression - Improvement scale (CGI_I) [5].

Both the developped predictive models can be summered in Equation 1 and Equation 2.

Predictive model 1: using only PANSS scores

$$\begin{aligned} EQ-5D_{it} &= \alpha + \beta_1 * PANSS\_POS_{it} \\ &+ \beta_2 * PANSS\_NEG_{it} \\ &+ \beta_3 * PANSS\_PSY_{it} \\ &+ \beta_{4,1} * AGE_{it} + \beta_{4,2} * AGE_{it}^2 \\ &+ \beta_5 * SEX_i + \beta_6 * FR_i \\ &+ \beta_7 * GE_i + u_i + e_{it}, \end{aligned} \quad (1)$$

where FR_i and GE_i are dummy variables for France and Germany.

For comparison, in a second step, $EQ-5D$ utility measure is replaced by $SF-6D$ utility measure in Equation 1.

Predictive model 2: using additional co-variables

$$\begin{aligned} EQ-5D_{it} &= \alpha + \beta_1 * PANSS\_POS_{it} \\ &+ \beta_2 * PANSS\_NEG_{it} \\ &+ \beta_3 * PANSS\_PSY_{it} \\ &+ \beta_{4,1} * AGE_{it} + \beta_{4,2} * AGE_{it}^2 \\ &+ \beta_5 * SEX_i + \beta_6 * FR_i + \beta_7 * GE_i \\ &+ \beta_8 * AP1_{it} + \beta_9 * AP2_{it} \\ &+ \beta_10 * CDSS_{it} + \beta_11 * GAF_{it} \\ &+ \beta_12 * CGI\_S_{it} + \beta_13 * CGI\_I_{it} \\ &+ u_i + e_{it}, \end{aligned} \quad (2)$$

where $AP1$=1 if AP is "Mixed", 0 otherwise ; $AP2$=1 if AP is "Only Atypical", 0 otherwise ; and the complement is when AP is "Only Typical".

For comparison, $EQ-5D$ utility measure is also replaced by $SF-6D$ utility measure in Equation 2.

[2] 9 items, from 0 (no problem) to 3 (very serious). Total score from 0 (no depression) to 27 (serious depression).

[3] VAS from 0 (bad) to 100 (good).

[4] 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating: 1=normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, extremely ill.

[5] 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

2.4 Statistical analysis

A panel model with random individual effects is used:

$$\begin{aligned} U_{it} &= \alpha + X_{it} * \beta + u_i + e_{it}, & (3) \\ u_i &\sim i.i.d.N(0, \sigma_u^2), & (4) \\ e_{it} &\sim i.i.d.N(0, \sigma_e^2), & (5) \end{aligned}$$

for $i = 1, \ldots, N$ the individual dimension, and $t = 1, \ldots, 5$ the time dimension. i corresponds to the patients and t to the visit number (1 to 5). U_{it} is the utility measure, X_{it} a row vector of explanatory variables. e_{it} is an error term specific to individual i at visit t. u_i is an error term specific to individual i.

3 Results

The three countries are pooled. STATA® software is used to estimate the models.

3.1 Descriptive statistics

Firstly, the descriptive statistics are presented in Table 1.

Secondly, the correlation structure of the explanatory variables is examined in Table 2. It can be shown that AGE^2 is strongly correlated with AGE (correlation coefficient equal to 0.99). Consequently, AGE^2 is not considered in our analysis.

3.2 Predictive model 1: using only PANSS scores

When $EQ-5D$ is used as dependent variable in Equation 1, the estimates are presented in Table 3.

When $SF-6D$ is used as dependent variable in Equation 2, the estimates are presented in Table 4.

3.3 Predictive model 2: using additional co-variables

For $EQ-5D$ as explanatory variable, the estimates are presented in Table 5.

For $SF-6D$ as explanatory variable, the estimates are presented in Table 6.

Table 1: Descriptive statistics

Variable	Obs	Mean	Std. Dev.	Min	Max
PANSS_POS	4840	11.8624	5.411375	7	40
PANSS_NEG	4842	15.39385	7.275326	7	43
PANSS_PSY	4851	27.98969	9.85216	16	80
AGE	4797	41.87034	10.93218	18.7041	67.0192
SEX	4843	.6208961	.4852141	0	1
FR	4864	.2090872	.4066986	0	1
GE	4864	.5193257	.4996777	0	1
AP1	4864	.1683799	.3742418	0	1
AP2	4864	.2732319	.4456647	0	1
CDSS	4846	2.448824	3.397407	0	21
GAF	4854	52.2981	23.35743	0	888
CGI_S	4863	3.820276	1.421244	1	7
CGI_I	3217	2.905502	1.837902	0	7

Table 2: Correlation structure

	PANSS_POS	PANSS_NEG	PANSS_PSY	AGE	AGE^2	SEX	AP1	AP2	CDSS	GAF	CGI_S	CGI_I
PANSS_POS	1.00											
PANSS_NEG	0.41	1.00										
PANSS_PSY	0.71	0.69	1.00									
AGE	0.00	0.03	0.01	1.00								
AGE^2	-0.02	0.02	-0.01	0.99	1.00							
SEX	0.10	0.10	0.07	-0.20	-0.19	1.00						
AP1	0.11	0.10	0.12	-0.05	-0.06	0.07	1.00					
AP2	-0.03	-0.09	-0.09	-0.23	-0.22	0.00	-0.32	1.00				
CDSS	0.22	0.20	0.43	-0.01	-0.03	-0.05	0.11	-0.04	1.00			
GAF	-0.38	-0.46	-0.43	-0.14	-0.12	-0.07	-0.15	0.09	-0.25	1.00		
CGI_S	0.47	0.49	0.52	0.07	0.05	0.09	0.12	-0.06	0.22	-0.51	1.00	
CGI_I	0.03	0.05	0.05	0.08	0.08	-0.01	-0.01	0.01	0.05	-0.13	0.11	1.00

Table 3: Predictive model 1: explaining EQ-5D using only PANSS scores

EQ-5D	Coef.	Std. Err.	z	$P > \|z\|$	[95%	Conf. Interval]
PANSS_NEG	.0029845	.0007695	3.88	0.000	.0014764	.0044926
PANSS_PSY	-.0094643	.0005603	-16.89	0.000	-.0105624	-.0083662
AGE	-.0020263	.0005141	-3.94	0.000	-.0030339	-.0010187
SEX	.0385409	.0117991	3.27	0.001	.015415	.0616668
FR	.0461008	.0141053	3.27	0.001	.0184549	.0737467
α	1.022786	.0269743	37.92	0.000	.9699169	1.075654

$PANSS\_pos$ and GE were not significant and were removed.
R^2: within = 0.0391, between = 0.1844, overall = 0.1207.
σ_u = .1627326, σ_e = .18410576, ρ = .43861029 (fraction of variance due to u_i).

Table 4: Predictive model 1: explaining SF-6D using only PANSS scores

SF-6D	Coef.	Std. Err.	z	$P > \|z\|$	[95%	Conf. Interval]
PANSS_NEG	.001901	.0003785	5.02	0.000	.0011592	.0026428
PANSS_PSY	-.0047881	.0002717	-17.62	0.000	-.0053207	-.0042556
AGE	-.0008214	.0002534	-3.24	0.001	-.001318	-.0003249
SEX	.018013	.0058486	3.08	0.002	.0065499	.029476
FR	.021031	.008302	2.53	0.011	.0047593	.0373027
GE	.0108555	.0066988	1.62	0.105	-.0022739	.023985
α	.8222745	.0138434	59.40	0.000	.7951419	.849407

$PANSS\_POS$ was not significant and was removed.
R^2: within = 0.0438, between = 0.1795, overall = 0.1333.
σ_u = .08067, σ_e = .08529752, ρ = .47213954 (fraction of variance due to u_i).

Table 5: Predictive model 2: explaining EQ-5D using additional co-variables

EQ-5D	Coef.	Std. Err.	z	$P > \|z\|$	[95%	Conf. Interval]
PANSS_NEG	.0035952	.0009314	3.86	0.000	.0017697	.0054207
PANSS_PSY	-.0047804	.0007641	-6.26	0.000	-.0062779	-.0032828
AGE	-.001944	.0005247	-3.70	0.000	-.0029724	-.0009155
SEX	.0400748	.0121405	3.30	0.001	.0162799	.0638697
FR	.029815	.0158133	1.89	0.059	-.0011785	.0608085
GE	.0342161	.0157342	2.17	0.030	.0033776	.0650546
α	.9214611	.0427594	21.55	0.000	.8376541	1.005268
CDSS	-.0196009	.001445	-13.56	0.000	-.0224331	-.0167688
GAF	.0008968	.0003696	2.43	0.015	.0001724	.0016211
CGI_S	-.0167873	.0047436	-3.54	0.000	-.0260846	-.00749
CGI_I	.0046193	.0022168	2.08	0.037	.0002745	.0089642

$PANSS\_POS$, $AP1$, $AP2$ were not significant and were removed.
R^2: within =0.0590, between = 0.3025, overall = 0.2111.
σ_u = .13237514, σ_e = .1890825, ρ = .32891706 (fraction of variance due to u_i).

Table 6: Predictive model 2: explaining SF-6D using additional co-variables

SF-6D	Coef.	Std. Err.	z	$P > \|z\|$	[95%	Conf. Interval]
PANSS_NEG	.0020917	.0003707	5.64	0.000	.0013652	.0028182
PANSS_PSY	-.0027665	.0002925	-9.46	0.000	-.0033398	-.0021931
AGE	-.000873	.0002318	-3.77	0.000	-.0013273	-.0004187
SEX	.0141953	.0053336	2.66	0.008	.0037417	.0246489
FR	.0130596	.0076754	1.70	0.089	-.0019838	.0281031
GE	.0196537	.0067626	2.91	0.004	.0063993	.0329081
α	.7910035	.0149548	52.89	0.000	.7616926	.8203144
AP1	-.0120222	.0048016	-2.50	0.012	-.0214332	-.0026112
CDSS	-.0095412	.0005595	-17.05	0.000	-.0106378	-.0084445
GAF	.000341	.0000889	3.84	0.000	.0001668	.0005153
CGI_S	-.0048595	.0020163	-2.41	0.016	-.0088113	-.0009077

$AP2$, CGI_I and $PANSS\_POS$ were not significant and were removed.
R^2: within = 0.0788, between = 0.3220, overall = 0.2364.
σ_u = .07010683, σ_e = .08379247, ρ = .41177171 (fraction of variance due to u_i).

4 Discussion and conclusion

Using data from the observational EuroSC cohort, we examined the predictors of utility measure in schizophrenic patients. Our study examined 1,208 patients with schizophrenia; controlled for important socio-demographic, clinical, and medication factors and has attempted to overcome the limitations of past studies by using a large sample size and a 24-month follow-up. Age, gender, PANSS psychopathology score, CDSS score, and prescription SGAs in comparison to FGAs were the most important predictors associated with utility.

Age affects negatively the utility measure. According to Kemmler et al. [1997], social problems, isolation and even stigmatization of schizophrenic patients tend to increase with age. Concerning gender, being a man affects positively the utility measure in our study. This finding appears in agreement with general literature, where women's quality of life is often reported lower than men's one, especially with regard to psychological and mental health domains (Reine et al. [2005]).

Looking at the influence of PANSS scores, we find that PANSS psychopathology factor negatively affects utility measure (P value < 0.001) whereas PANSS Positive and negative factors does not affect or affects moderately utility measure. In the same way as PANSS psychopathology factor, CDSS score negatively affects utility measure (P value $<$ 0.001). These findings are coherent with several meta-analyses which revealed that symptoms have only a modest relationship with quality of life, and that general psychopathology symptoms (e.g., anxiety and depression) were the most important predictors (Eack and Newhill [2007]).

Finally, patients treated with FGAs were associated to a lower utility in comparison with SGAs. This result seems coherent as SGAs have been shown to be superior to FGAs in terms of treatment of negative symptoms, cognitive enhancement, fewer extra-pyramidal symptoms, tolerability, and higher levels of subjective well-being (Fenton et al. [1997]). The burden of side-effects has been extensively explored as a predictor of poor medication adherence and relapse.

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