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### Introduction

Over the past few decades the study of Quality of Life (QoL) penetrated many areas of clinical research. We can find a consensus requiring the assessment of Quality of Life in clinical medicine as a one of the basic requirements in different medical and health intervention settings. In this study we present multivariate analysis of Quality of Life data in patients admitted to the regional hospital in Ústí nad Orlicí with the diagnosis of inflammatory bowel disease called Crohn's disease. The analysis uses the World Health Organization's quality of life questionnaire that helped identify principal determinants of the Quality of Life in Crohn's disease patients.

A primary reason for adopting the multivariate approach is quite intuitive, since the outcome variables related to Quality of Life assessment clustered naturally into four distinct domains characterizing patient's Physical Health, Psychological Health, Social Relationships and Patient's Environment. In this paper we are thus primarily concerned with multivariate analysis of the Quality of Life of Crohn's disease patients which assumes a joint multivariate normal distribution of the four Quality of Life domains. Multivariate and marginal analyses based on the multivariate model are coupled with those examining the overall Quality of Life score, hence the advantage of the multivariate approach is illustrated. Finally, a better insight into the relationship between individual QoL domains and the predictors appearing in the final multivariate model is achieved via studying linear contrasts based on the final multivariate model. They provide valuable information regarding differential response in individual domains. As an alternative to analyzing the overall Quality of Life score, multivariate analysis uses all available information whereby increasing power to detect influential QoL determinants, while maintaining the distinction between the individual Quality of Life domains.

### Medical Background

Crohn's disease is an inflammatory bowel disease affecting patients across a wide range of ages. In this study we assessed Quality of Life of Crohn's disease patients by modelling the scores related to physical and psychological health, social relationships and factors attributable to subjects' environment. In addition to the anticipated relation with the extent of Crohn's disease itself, measured by the Crohn's Disease Activity Index (CDAI), the Quality of Life of Crohn's disease patients was likely to be influenced by treatment options assigned to individual patients. These may, for instance, include surgery history, use of immunosuppressants and/or corticoids. Gender and age are also likely modifiers of patient's experience with the disease and its course. Other candidate determinants of Quality of Life included factors describing subject's social-economic status, education, smoking habits, marital status etc. Furthermore, maximal location of the disease prior to surgery and the disease behaviour could also well represent possible determinants of patient's quality of life, although some of this information is necessarily captured by the CDAI.

### Methods

We used localized, officially translated and licensed version of the WHOQoL-BREF questionnaire that included twenty-six specific questions on the topics related to the four domains characterizing physical and psychological health of the subject, his or her social relationships and subject's environment. Individual integer scores ranged on a scale between one and five. Seven of the twenty-six scores were related to physical domain, six described psychological health, three were related to social relationships and eight described patient's environment. Average of the scores falling within the same domain was transformed to a scale of 4 through 20 and used to describe a Quality of Life measure associated with a particular domain. The same scale was used for the overall mean Quality of Life score. Following the central limit theorem, each of the four average scores followed approximately univariate normal distribution with the corresponding mean and variance that needed to be estimated from the data. Similarly, the overall Quality of Life score approximately followed univariate normal distribution, allowing for standard linear models-based inference.

Furthermore, since each of the four domains described a single dimension in the total Quality of Life space, it was rather natural to consider multivariate normal model for our data with each domain representing one dimension in the four-dimensional Quality of Life space. Methods appropriate for statistical inference based on models for multivariate normally distributed outcomes were applied.

### Results

Multivariate analysis identified four predictors that explained significant amount of variability within all four domains of Quality of Life. The strongest explanatory variable appeared to be CDAI (Crohn's Disease Activity Index), followed by interaction between gender and use of corticoids, main effect of gender and that of immunosuppression and corticoids use. All model predictors appeared to be significant at the significance level  $\alpha = 0.01$ . Summary of the results is shown in Table 1.

**Table 1:** Multivariate ANOVA of Quality of Life Domains

Model predictors	DF	Pillai-Bartlett	F(4,94)	Pr(>F)
Intercept	1	0.99	2167.62	<0.0001
CDAI (1 unit change)	1	0.39	14.87	<0.0001
Gender	1	0.15	4.08	0.0043
Immunosuppression	1	0.14	3.87	0.0059
Use of Corticoids	1	0.14	3.69	0.0078
Gender:Corticoids Use <sup>†</sup>	1	0.16	4.63	0.0019
Residuals	97			

<sup>†</sup> Interaction term

As an alternative to the multivariate approach, one could consider univariate ANCOVA model for an overall QoL score that would average the QoL experience across all four domains. However, the corresponding ANOVA would not identify interaction between the effect of Gender and the Use of Corticoids ( $p=0.672$ ). Averaging the QoL experience across all four domains would have resulted in the loss of information otherwise available from individual QoL domains. Specifically, if multivariate analysis was not adopted, a differential gender-related response to the Use of Corticoids within individual domains would have remained unnoticed.

Since all of the predictors were associated with one degree of freedom, all corresponding multivariate tests, that is 'Wilks', 'Roy', 'Hotelling-Lawley' and 'Pillai-Bartlett', were equivalent and thus rendered identical results.

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**Table 2:** Differences in the QoL Scores within Individual QoL Domains - univariate analyses based on the multivariate model

FACTOR	Score difference per QoL Domain (p-value)			
	Physical	Psychological	Social	Environmental
CDAI (1 unit change)	-0.019 (<0.001)	-0.014 (<0.001)	-0.010 (<0.001)	-0.009 (<0.001)
Male Gender	-0.652 (0.273)	1.540 (0.004)	0.321 (0.603)	0.095 (0.823)
Immunosuppression	-0.937 (0.146)	-2.127 (<0.001)	-1.825 (0.007)	-1.822 (<0.001)
Use of Corticoids	-1.179 (0.161)	2.801 (<0.001)	1.476 (0.092)	1.100 (0.068)
Male Gender:Corticoids Use <sup>†</sup>	2.054 (0.052)	-1.986 (0.032)	-1.297 (0.236)	-0.593 (0.428)

<sup>†</sup> Interaction term

### Main Effects Summary

As we may observe from Table 2, Quality of Life decreased consistently with the disease progression (CDAI) across all four domains and its highest impact was observed within physical and psychological domain, which was to be expected. Immunosuppression also had a consistent effect across all four domains, reducing the overall QoL levels as compared with patients not on immunotherapy. In relation to immunosuppression treatment, the lowest QoL scores were observed within psychological domain ( $d = -2.127$ ,  $p < 0.001$ ), followed about equally by social ( $d = -1.825$ ,  $p = 0.007$ ) and environmental domain ( $d = 1.822$ ,  $p < 0.001$ ), while the physical domain appeared to be affected the least ( $d = -0.937$ ,  $p = 0.146$ ).

### Gender-specific Effect of Corticoids Treatment

The effect of the use of corticoids on the QoL appeared to be modified by gender. Within the physical domain the use of corticoids in female subjects was associated with insignificantly reduced levels of QoL ( $d = -1.179$ ,  $p = 0.161$ ), while within other three domains it appeared consistently positive. Within psychological domain, in particular, the use of corticoids elevated the overall QoL levels in female subjects by  $d = 2.801$  on average ( $p < 0.001$ ), while within social ( $d = 1.476$ ,  $p = 0.092$ ) and environmental domain ( $d = 1.1$ ,  $p = 0.068$ ) the corresponding increase appeared only marginally significant.

In male subjects the use of corticoids appeared to be consistently beneficial in terms of the QoL, although in no case it reached the level of statistical significance. Within the physical and psychological domain, respectively, the QoL levels increased by  $d = 0.876$  and  $d = 0.815$  ( $p = 0.217$  and  $0.190$ ), while the corresponding increase within social and environmental domain was only of the order of  $0.179$  and  $0.507$  ( $p = 0.808$  and  $0.317$ ), respectively.

### Therapy-specific Gender Differences

Among the subjects not receiving corticoid therapy the only gender-related statistically significant difference in the QoL scores was observed for psychological domain, in which the male subjects appeared to have enjoyed higher levels of QoL than female ones ( $d = 1.540$ ,  $p = 0.004$ ). All other gender-related differences among those not receiving corticoid therapy appeared statistically insignificant. Among the subjects who were assigned the corticoid therapy, all gender-related differences in the QoL scores appeared statistically insignificant.

### Contrasts Assessment using Multivariate Model for QoL

We evaluated a linear contrast in the QoL scores comparing the physical domain with the three remaining domains. Sphericity assumption, which may be viewed as an extension of the concept of equality of variance in the traditional ANOVA experiments, was not satisfied for our data. The use of approximate statistics (Greenhouse-Geisser, Huynh-Feldt) was therefore not warranted and multivariate tests were adopted instead. This analysis helped identify those factors among the model predictors that are primarily responsible for differential response within the two segments of the QoL space.

**Table 3:** Analysis of Contrasts Comparing the Physical vs. Remaining Three Domains

Model predictors	DF	Pillai-Bartlett	F(1,97)	Pr(>F)
Intercept	1	0.1083	11.78	0.0008
CDAI (1 unit change)	1	0.1472	16.74	<0.0001
Gender	1	0.0119	1.17	0.2818
Immunosuppression	1	0.0152	1.50	0.2233
Use of Corticoids	1	0.0348	3.50	0.0645
Gender:Corticoids Use <sup>†</sup>	1	0.1060	11.50	0.0010
Residuals	97			

<sup>†</sup> Interaction term

### Discussion

Analysis of contrasts shown in Table 3 confirmed our previous finding of a differential QoL response in male and female subjects with regard to the use of corticoids, which manifested itself within the first and the remaining three QoL domains ( $p=0.0010$ ). While in women the use of corticoids appeared to have an adverse effect within the physical domain, psychological, social and environmental domain were all affected positively.

We also employed traditional sets of simultaneous contrasts comparing all three pairs of within-subject contrasts between the QoL dimensions, rendering inference similar as shown above. Tables 1 and 3 suggest that obtaining a correct inference regarding gender-related response to corticoid treatment would not be possible without adopting multivariate approach.

### References

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