



Paper Accepted\*

ISSN Online 2406-0895

Original Article / Оригинални рад

Tamara Babić<sup>1,†</sup>, Igor Dragičević<sup>2</sup>, Aleksandar Ćorac<sup>3</sup>,  
Goran Trajković<sup>4,5</sup>, Luka Nikolić<sup>6</sup>, Miloš Bjelović<sup>1,5</sup>

### Gastroesophageal Reflux Disease and Functional Dyspepsia: What is the real Burden on Health Related Quality of Life?

Поређење квалитета живота повезаног са здрављем код болесника са гастроезофагеалном рефлуксном болести и функционалном диспепсијом

<sup>1</sup> Department for Minimally Invasive Upper Digestive Surgery, University Clinic for Digestive Surgery – First Clinical Surgical Hospital, Clinical Center of Serbia, Belgrade, Serbia

<sup>2</sup> Public Health Institute, Šabac, Serbia

<sup>3</sup> School of Medicine, University of Pristina, Kosovska Mitrovica, Serbia

<sup>4</sup> Institute for medical statistics, School of Medicine, University of Belgrade, Belgrade, Serbia

<sup>5</sup> School of Medicine, University of Belgrade, Belgrade, Serbia

<sup>6</sup> Edinburgh Medical School: Biomedical Sciences, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, United Kingdom

Received: April 10, 2017

Revised: December 10, 2017

Accepted: December 12, 2017

Online First: December 22, 2017

DOI: <https://doi.org/10.2298/SARH170419205B>

\* **Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal.

The date the article was made available online first will be carried over.

† **Correspondence to:**

Tamara BABIĆ

Department for Minimally Invasive Upper Digestive Surgery, University Clinic for Digestive Surgery – First Clinical Surgical Hospital, Clinical Center of Serbia, Dr Koste Todorovica Street N0 6, 11 000 Belgrade, Serbia

E-mail: [b.tamara86@gmail.com](mailto:b.tamara86@gmail.com)

## Gastroesophageal Reflux Disease and Functional Dyspepsia: What is the real Burden on Health Related Quality of Life?

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### SUMMARY

**Introduction/Objective** Recently published studies have addressed the significant impairment of Health Related Quality of Life (HRQoL) in patients suffering from gastroesophageal reflux disease (GERD) and functional dyspepsia (FD). To the best of our knowledge, none of previously published studies has compared the impact of GERD and FD on HRQoL.

The aim of the study was to determine impact of GERD and FD on HRQoL.

**Methods** The current sample was extrapolated from a large cross-sectional population based study conducted in primary health care facilities. Primary care physicians (PCPs) and general internists (GI) diagnosed GERD according to the Montreal definition for population-based studies. Also, PCPs and GI diagnosed FD based on the Rome III criteria. The Serbian version of the generic self-administered Center for Disease Control and Prevention questionnaire (CDC-HRQOL-4) was used. We used the propensity score method (PSM) to match GERD and FD samples on variables such as age, gender, education and adherence to therapy.

**Results** Regarding self-rated health, similar results were obtained from both groups. The CDC-HRQOL-4 further revealed that functional dyspepsia led to greater disturbances of every-day functioning in regards to the criteria of physically healthy, mentally healthy, and activity limitation days.

**Conclusion** The results of the study have shown significant impairment of HRQoL in both groups, but surprisingly patients with functional dyspepsia experienced more limitations to their every-day functioning compared to patients with gastroesophageal reflux disease.

**Keywords:** quality of life; gastroesophageal reflux; functional dyspepsia; population study; surveys and questionnaires

### САЖЕТАК

**Увод/Циљ** Недавно објављене студије показале су нарушење квалитета живота повезаног за здрављем (КЖПЗ) код пацијената са дијагностикованом гастроезофагеалном рефлуксном болести (ГЕРБ) и функционалном диспепсијом (ФД). Прегледом доступне литературе нисмо нашли студију која се бави поређењем утицаја ове две хроничне неразазне болести на КЖПЗ.

Циљ рада је био да упореди КЖПЗ болесника са дијагностиковом ГЕРБ и ФД.

**Метод** Студијом су обухваћена 1236 испитаника са дијагностикованом ГЕРБ и ФД. Тренутни узорак је екстраполиран из велике студије пресека која је спроведена у установама примарне здравствене заштите у Србији. ГЕРБ је дијагностикована према Монреалској дефиницији болести за популационе студије. ФД је дијагностикована према Римским III критеријумима. У испитивању је коришћена српска верзија општег упитника за процену КЖПЗ Центра за контролу и превенцију болести у Атланти. Коришћене су методе дескрипционе статистике као и метод скор подударности поређењем варијабли као што су старост, пол, ниво образовања и узимање терапије.

**Резултати** Поређењем тренутног здравственог стања испитаника, слични резултати су добијени у обе групе. Даљом анализом утврђено је да испитаници са дијагностикованом ФД имају у већој мери нарушен КЖПЗ у доменима физичког и менталног здравља и обављању уобичајених активности у односу на испитанике са ГЕРБ.

**Закључак** Резултатима студије показано је озбиљно нарушење КЖПЗ у обе групе испитаника, са тим да у неким доменима свакодневног живота испитаници са ФД имају веће нарушење КЖПЗ у односу на пацијенте са дијагностикованом ГЕРБ.

**Кључне речи:** квалитет живота; гастроезофагеални рефлукс; функционална диспепсија; популациона студија; анкете и упитници

### INTRODUCTION

It has been estimated that gastroesophageal reflux disease (GERD) and functional dyspepsia (FD) represent the most common gastrointestinal diseases in the general population, with a rising prevalence worldwide [1, 2]. While heartburn is a cardinal symptom of gastroesophageal reflux disease (GERD), there is consensus that abdominal discomfort or pain centered in the upper abdomen as well as an absence of any organic esophageal lesions is a primary symptom of functional dyspepsia

(FD). Abdominal pain or discomfort is often associated with bloating, nausea, heartburn, vomiting etc. [3]. Although not life threatening, patients with GERD or FD perceive the effects of their condition to a similar degree to patients with other serious chronic diseases [4, 5].

Recently published studies have addressed the significant impairment of Health Related Quality of Life (HRQoL) in patients suffering from GERD, in the areas of eating and drinking, physical activity, psychological wellbeing, as well as reduced vitality and poor sleep [6,10]. Furthermore, studies have shown that the direct costs of GERD range between PPP\$172 (purchasing power parity in US dollars) and PPP\$176 per person per year, thus causing a substantial economic burden [11, 12]. On the other hand, FD has been shown to significantly reduce HRQoL in the domains of general health, vitality, and the emotional and mental health of the patients compared to the general population [13, 14]. A study analyzing patient-reported costs and claims in the USA found that FD patients incurred additional expenses of more than US\$ 2000/year [15].

Although the previously published studies have addressed the significant impairment in HRQoL domains in patients suffering from GERD and FD separately, to the best of our knowledge none of them have compared the impact of GERD and FD on HRQoL.

The aim of this study was to distinguish which of these two diseases has a greater impact on the HRQoL of affected patients.

## **METHODS**

The current sample was extrapolated from a large cross-sectional population based study conducted in primary health care facilities in urban and rural areas of Serbia, regarding the HRQoL of patients suffering from chronic non-transmittable diseases. The inclusion criteria were as follows: patients of both sexes, aged 18-90 years, willing and able to participate in this study and complete the questionnaire.

GERD was diagnosed by PCPs and GI according to the Montreal definition of GERD for population based studies, which included patients with mild symptoms of heartburn and/or regurgitation occurring at least two days per week, or moderate/severe symptoms of heartburn and/or regurgitation occurring at least one day per week [16]. FD was also diagnosed by PCPs and GI based on the Rome III criteria for FD, and encompassed patients with at least one of the following symptoms: postprandial fullness, early satiety, epigastric burning, and epigastric pain; occurring for the last 3 months with onset of symptoms at least 6 months prior to participating in the study [17]. The FD group included both patients with postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). Classification of GERD and FD was performed according to the International Classification of Diseases, Tenth Revision (ICD-10). Exclusion criteria included other significant upper gastrointestinal disorders and complications of GERD, as well as other chronic non-transmittable diseases, which are known to greatly impair HRQoL (diabetes mellitus, angina pectoris,

depression, chronic obstructive pulmonary disease, etc.) [18]. Inclusion and exclusion criteria ensured that only patients with GERD and FD were eligible for study participation.

The current study was approved by the local Ethics committee. Written informed consent was obtained from all participants prior to study participation.

In the current study, the Serbian version of the generic self-administered Center for Disease Control and Prevention questionnaire (CDC-HRQOL-4) was used. The questionnaire is divided into three sets of questions regarding general well-being, usual activities limitations including work and leisure activities and disease symptoms [30]. The participants of the study completed the questionnaire in the office of their PCPs. Previously published surveys had demonstrated that results from the CDC-HRQOL-4 questionnaire had good test/retest reliability and strong internal validity [19,20]. In this respect, the questionnaire has an advantage over other HRQoL instruments with more difficult methodology and limited practical value [21].

### **Statistical analysis**

We used the propensity score method (PSM) to match GERD and FD samples on variables such as age, gender, education and adherence to therapy. The PSMATCH 2 Stata module was used for propensity scoring with one-to-one nearest neighbor matching on the following covariates: age, gender, education and therapy administration [22]. The PSMATCH 2 Stata technique was first published by Rosenbaum and Rubin and represents a matched sampling method used to remove bias due to potential confounding factors [23]. This matching technique is used mainly for analyzing causal effects in intervention studies; however, it is also used in typical observational studies, including those with a cross-sectional design.

The descriptive statistics, including the mean and standard deviation of numerical data, as well as the numerical values and percentages of categorical variables, were used to characterize the study sample. The Pearson Chi-square test was used to compare categorical variables between the GERD and FD populations, and the independent samples t-test and the Mann-Whitney *U* test were used for the numerical variables. The level of significance was set at  $\alpha=0.05$ . The statistical analysis was performed using SPSS version 20.

## **RESULTS**

The response for this survey was over 90%. The 2472 participants that were suitable for analysis were divided into two groups based on the inclusion and exclusion criteria (1236 diagnosed with GERD and 1236 diagnosed with FD). All included participants were Caucasian. The sociodemographic characteristics of the participants are summarized in table 1. The study included 593 (48%) males, 643 (52%) females in GERD group, 599 (48.5%) males, and 637 (51.5%) females in FD group. Mean age in GERD group was 50.8 years in GERD group and 50.5 years in FD group. There was no statistically significant difference regarding gender, age, level of education and therapy

**Table 1. Sociodemographic characteristics.**

	GERD (n=1236)	FD (n=1236)	<i>p</i>
<b>Gender, n (%)</b>			
Male	593 (48.0)	599 (48.5)	0.809
Female	643 (52.0)	637 (51.5)	
<b>Age (years), mean ± SD</b>	50.8±14.1	50.5±14.3	0.670
<b>Education, n (%)</b>			
Lower education level	175 (14.2)	181 (14.6)	0.982
Higher education level	1061 (85.8)	1055 (85.4)	
<b>Therapy administration, n (%)</b>			
No	29 (2.3)	34 (2.8)	0.803
Yes, OTC medication	96 (7.8)	98 (7.9)	
Yes, administered by PCP	1111 (89.9)	1104 (89.3)	

OTC- over the counter; PCP- primary care physician

**Table 2. Self-rated health of patients in GERD and FD group.**

Characteristics	GERD	FD	<i>p</i>
<b>Self-rated health n (%)</b>			
Excellent, very good, good	677 (55.3%)	709 (58.2%)	0.155
Fair, poor	547 (44.7%)	510 (41.8%)	
<b>Number of unhealthy days, (mean ±SD)</b>			
Unhealthy days	10.7±10.6	11.9±10.5	<b>0.005</b>
Physically unhealthy days	6.7±7.5	7.3±7.2	<b>0.005</b>
Mentally unhealthy days	5.4±7.4	6.3±7.5	<b>&lt;0.001</b>
Activity limitation days	4.4±6.9	5.3±7.3	<b>0.001</b>
<b>Patients with ≥14 unhealthy days, n (%)</b>			
Unhealthy days	314 (25.4%)	374 (30.3%)	0.007
Physically unhealthy days	194 (15.7%)	192 (15.5%)	0.912
Mentally unhealthy days	151 (12.2%)	158 (12.8%)	0.670
Activity limitation days	125 (10.1%)	139 (11.2%)	0.362

**Table 3. Duration of symptoms during the past 30-days.**

Symptoms	GERD	FD	<i>p</i>
<b>Duration of symptoms, (mean ±SD)</b>			
Pain limitation days	5.1±6.4	5.4±6.5	0.159
Days with depression	6.1±7.8	5.8±7.2	0.919
Days with anxiety	7.0±7.6	7.3±7.7	0.463
Days with poor sleep	7.2±7.6	8.4±7.7	<b>&lt;0.001</b>
Days with good health	12.4±10.0	11.9±9.5	0.375
<b>Patients with ≥14 unhealthy days, n (%)</b>			
Pain limitation days	114 (9.2%)	128 (10.4%)	0.343
Days with depression	137 (11.1%)	114 (9.2%)	0.126
Days with anxiety	150 (12.1%)	172 (13.9%)	0.189
Days with poor sleep	160 (12.9%)	209 (16.9%)	0.006
Days with good health	351 (28.4%)	350 (28.2%)	0.964

administration between two groups. The education level of the participants was classified based on the International Standard Classification of Education into lower education level, which included participants with no education or primary education only; and higher education level, which included participants with secondary education, tertiary and post-tertiary education.

Self-rated health and number of unhealthy days are shown in table 2. Regarding current health status 547 (44.7%) patients in GERD group self-rated their health as fair or poor compared to 510 (41.8%) of patients in FD dyspepsia group ( $p>0.05$ ). Mean number of mentally unhealthy days was 5.4±7.4 days in GERD group versus 6.3±7.5 days in FD group ( $p<0.01$ ). Mean number of activity limitation days was 4.4±6.9 in GERD group compared to 5.3±7.3 days in FD group ( $p=0.001$ ).

There was no statistically significant difference between the two groups regarding the participants self-rated health in the past 30 days. In other criteria however, there was a statistically significant difference observed between the two groups, all in favor of FD. The differences were specifically in the criteria regarding unhealthy days in the past 30 days, physically unhealthy days in

the past 30 days, mentally unhealthy days in the past 30 days, and activity limitation days in the past 30 days.

In GERD group mean number of days with poor sleep during the past 30-days was  $7.2 \pm 7.6$  compared to  $8.4 \pm 7.7$  in FD group ( $p < 0.001$ ). Regarding physical pain, 114 (9.2%) patients had  $\geq 14$  pain limitation days compared to 128 (10.4%) patients in FD group.

On further analyzing the occurrence of symptoms in the past 30 days, a statistically significant difference was observed regarding days with poor sleep, once again in favor of FD (Table 3).

## DISCUSSION

GERD and FD represent the most prevalent conditions in patients seeking a medical consultation for abdominal symptoms [24]. Traditionally, medical practitioners are focused on objective clinical findings and their treatment, while patients are mostly concerned with their symptoms. This difference is particularly important in cases of non-erosive reflux disease (NERD) and FD, the distinguishing features of which are the absence of objective endoscopic findings. Thus, measuring HRQoL provides additional information beyond what could be obtained by standard clinical examination.

Indeed, studies have demonstrated that both GERD and FD carry a significant burden regarding impaired HRQoL in the domains of general health, mental and emotional well-being, as well as lower work productivity [25]. Unfortunately, none of these studies have compared the diseases regarding their effect on HRQoL, nor had they determined which disease patients on average deemed more troublesome.

To the best of our knowledge, this is the first study of this type worldwide. The validation of this study was achieved using adequate study methodology and reliable self-administered generic CDC-HRQOL-4 questionnaire. The questions, despite their brevity, captured the key concepts of health as defined by The World Health Organization (WHO) back in 1948, “a state of complete physical, mental, and social well-being –not merely the absence of disease or infirmity” [26]. Today there are many validated disease-specific instruments for GERD and FD. However, disease-specific instruments do not allow for comparisons with illnesses other than GERD and FD, nor with healthy individuals in the general population. Therefore, generic HRQoL measures are valuable to supplement disease-specific instruments and enable comparison between two different diseases.

Over ninety percent of participants who were asked to participate in this study completed a questionnaire. This is a representative sample of those affected by GERD and FD in general population in Serbia. The previous studies reported the prevalence of overlap of GERD with FD around 7.5-8.4% especially in cases of NERD [27]. Unrecognized syndrome overlap was thought to be an important factor in partial or complete proton pump inhibitor (PPI) failure in GERD therapy. While the Rome II classification of functional gastrointestinal disorders (FGD) classified syndromes by their prominent symptoms, it failed to identify sub-groups with homogenous underlying

pathophysiological mechanism [28]. After further pathophysiological studies, the Rome III criteria were developed to identify and distinguish different syndromes within the FGD group, especially FD [29]. To minimize the chance of syndrome overlapping both GERD and FD were classified according to current the Montreal and Rome III protocols. Furthermore, statistical analysis showed no statistically significant difference between either of the groups regarding the use of self-administered over-the-counter (OTC) medication and medication prescribed by the PCPs, hence excluding the PPI failures as potentially unrecognized FD patients.

In our study, there was no statistically significant difference between the two groups regarding sociodemographic characteristics. All the domains comprising the CDC-HRQOL-4 questionnaire were significantly impaired in both groups, with unhealthy days, physically unhealthy days, mentally unhealthy days, and activity limitation days, as the areas of most marked disturbance. These results are consistent with previously published results [6, 13]. The “unhealthy days” variable has continuous, cardinal, and bounded (range=0 to 30 days) mathematical properties and represents the briefest validated set of generic HRQoL measures, with minimal overlap with the “physically” and “mentally unhealthy days” variables in comparison with other instruments, hence reliably describing HRQoL oscillations over a period of time. Regarding self-rated health, similar results were obtained from both groups [30].

The CDC-HRQOL-4 questionnaire further revealed that FD led to greater disturbances of every-day functioning in regards to the criteria of physically healthy, mentally healthy, and activity limitation days [6, 13]. Patients with FD experienced more days with poor sleep compared to the GERD group. Sleep disorders are quite common medical problems, and have been associated with several diseases, including GERD and FD [10].

## CONCLUSION

The results of the study have shown significant impairment of HRQoL in both groups, but surprisingly patients with FD experienced more limitations to their every-day functioning in areas of HRQoL compared to patients with GERD. Thus, while often underestimated and considered a minor public health problem compared to other chronic diseases, FD confers a significant burden to patients' HRQoL. We believe that the results of this study have offered insight into the complex relationship between GERD, FD and HRQoL impairment. A better understanding of these mechanisms may allow for better disease management in the future.

This study has several limitations. Firstly, the results reflected the status of the predominantly Caucasian population of single country (Serbia). Another possible limitation is that the generic HRQoL instruments used to measure health domains tend to be more physical or mobility-based. Although the CDC-HRQoL-4 questionnaire allowed for comparison of two different diseases regarding their effect on HRQoL, unfortunately we were unable to determine which symptoms

patients with GERD and FD deemed most troublesome. Hopefully, this will be investigated in further studies.

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