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Do patients with chronic low-back pain experience a loss of health-related quality of life? A protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Health-related quality of life in chronic low back pain (LBP) is an important issue since various individual factors such as perceived loss of autonomy, inability to continue daily life and anxiety can contribute to maintenance or deterioration of this condition. Health-related quality of life is also important because it can predict the probability of recovery or recrudescence over time. In the literature, there is no systematic review on this topic. The present paper describes a protocol of the first systematic review and meta-analysis aimed at summarising the data on health-related quality of life in patients with chronic LBP compared with healthy controls. Gender, age and comorbidity of psychiatric disorders (mood or anxiety disorders) will be explored as moderators. Studies will be included if they used a case–control design comparing adults with chronic LBP to healthy controls on health-related quality of life through validated interviews/questionnaires.

Methods and analysis According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses, a systematic review and meta-analysis will be conducted from 10th to 17th January 2020. Independent reviewers will search published/unpublished studies through electronic databases (Scopus, PubMed, EMBASE and the Cochrane Library) and additional sources, will extract the data and assess the methodological quality through the Newcastle-Ottawa Scale. Random-effect meta-analysis will be carried out by calculating effect sizes as Cohen's d indices. Publication bias will be assessed and moderators of the effect sizes will be investigated through weighted least squares meta-regression.

The knowledge whether health-related quality of life is better or worse as a function of some individual characteristics may suggest personalised care pathways according to a precision medicine approach.

Ethics and dissemination The current review does not require ethics approval. The results will be disseminated through publications in peer-reviewed journals.

PROSPERO registration number CRD42019131749

Strengths and limitations of this study

- A search of both published and unpublished literature.
- Selection of the studies and extraction of the data performed by two independent reviewers.
- A methodological quality assessment will be conducted.
- Gender, age and psychiatric comorbidity will be investigated as predictors.
- A limitation may be the heterogeneity of the instruments to assess health-related quality of life.

INTRODUCTION

Chronic pain has been recognised as pain that persists past normal healing time and hence lacks the acute warning function of physiological nociception.[1] Low-back pain (LBP) is defined as pain of musculoskeletal origin extending from the lowest rib to the gluteal fold that may at times extend as somatic referred pain into the thigh (above the knee).[2] It is commonly accompanied by pain in one or both legs and some people with LBP have associated neurological symptoms in the lower limbs.[3] Chronic LBP is defined as LBP lasting more than 12 weeks.[4]

LBP can be classified as non-specific LBP, specific LBP and radiculopathy.[4] Non-specific LBP is defined as LBP not attributable to a known cause[5] and represents 90%–95% of the cases of LBP.[6] Specific LBP can be further classified according to specific spine disorders: trauma, malignancy, infections, inflammatory disorders, vascular and intra-abdominal causes and disc degenerative disease and spondyloarthritis.[7 8] Another relevant classification system considering the predominant mechanism of pain, classifies LBP in neuropathic, nociceptive, central sensitisation or psychogenic pain.[9]

The most accepted diagnostic criterion for LBP is presence of pain in the low back in the last 4 weeks, bad enough to limit usual activities or to change daily routine for more than 1 day.[2] According to Delitto *et al*,[9] other

important diagnostic criteria including physical examination are: (1) chronic, recurring LBP that is commonly associated with referred lower extremity pain and (2) presence of 1 or more of the following: low back and/or low back-related lower extremity pain that worsens with sustained end-range movements or positions, lumbar hypermobility with segmental motion assessment, mobility deficits of the thorax and lumbopelvic/hip regions, diminished trunk or pelvic region muscle strength and endurance and movement coordination impairments while performing community/work-related recreational or occupational activities.

Chronic LBP is one of leading causes of disability for adults of working age.[10] Globally, years lived with disability caused by chronic LBP increased by 54% between 1990 and 2015, mainly because of population increase and ageing.[11] It affects all age groups and is generally associated with sedentary occupations, smoking, obesity and low socioeconomic status.[12] In a recent systematic review[13] on 28 studies, chronic LBP prevalence was 4.2% in individuals aged between 24 and 39 years old and 19.6% in those aged between 20 and 59. Of the nine studies including individuals aged 18 years old or older, six reported chronic LBP between 3.9% and 10.2% and three reported prevalence between 13.1% and 20.3%. In more than 85% of cases of chronic LBP, the condition is best defined as non-specific LBP. Recurrence is very common and in a small proportion of people, LBP becomes persistent and disabling.[11] Initial high pain intensity, psychological distress and accompanying pain at multiple body sites increase the risk of persistent disabling LBP. Comorbid psychiatric disorders such as mood or anxiety disorders are more common among patients with chronic LBP than among persons without this clinical condition.[11 12]

Health-related quality of life is poorer in patients with chronic LBP than in healthy individuals.[13–15] Several factors can affect negatively health-related quality of life such as a negative self-perception in social interactions, with shame and frustration regarding difficulties to perform activities of daily living. Patients often feel misunderstood and unsupported, partly due to the absence of visible signs of the condition and suffer from the negative collective image attached to this condition as 'benign/psychological disease'.[16] The impact of chronic LBP on the person's life may decrease his/her self-esteem and self-efficacy due to the loss of autonomy and the inability to have or continue daily life/work activities.[17 18] The experience of chronic LBP is characterised by a conflict between the desire for self-efficacy, a sense of isolation and the paradoxical need to rely on others.[19] Chronic LBP is frequently accompanied by increased anxiety and the so-called mental defeat.[20] Health-related quality of life is also important because it can predict the probability of recovery over time in chronic LBP[21 22] and only about 40% of patients achieve complete recovery at 12 months. In the literature, there is no systematic review collecting the current data on this topic.

The present paper describes a protocol of the first systematic review and meta-analysis aimed at providing a quantitative summary of health-related quality of life in patients with chronic non-specific LBP compared with healthy controls. Gender, age and comorbidity of psychiatric disorders (mood or anxiety disorders) will be explored as predictors of the evidence, if significant heterogeneity is found. The rationale for investigating these predictors is based on the literature showing that: (1) female patients with musculoskeletal pain report more severe pain, lower quality of life, higher disability and higher comorbidity levels of psychiatric disorders than men, (2) older patients report more severe pain and stronger disability, (3) comorbidity of psychiatric disorders (mood and/or anxiety disorders) is higher among patients with chronic LBP than controls and it is associated with more severe pain and disability and more dysfunctional coping.[23–27] The knowledge whether health-related quality of life is better or worse according to individual characteristics may suggest personalised care pathways based on a precision medicine approach.

METHODS

The systematic review protocol has been presented according to the guidelines established in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P)[28] and was registered in PROSPERO on CRD42019131749. Any amendments will be updated on PROSPERO and documented accordingly.

Eligibility criteria

In agreement with the PRISMA guidelines,[29] the criteria considered for inclusion of studies will be related to (1) participants, (2) outcomes, (3) comparators and (4) design. Studies will be included if (1) they are conducted on adult clinical groups aged 18 years old or older with a primary diagnosis of chronic LBP; (2) they report quantitative data on differences in the levels of health-related quality of life between a group of patients with chronic non-specific LBP and a healthy control group or the authors are willing to provide the necessary data when contacted if such data are missing in the paper; (3) they report any definition of chronic LBP (we will accept the definitions of back pain provided in the included studies and we will report these as an outcome of the review); (4) they measured health-related quality of life through a validated standardised interview or a validated self-report questionnaire (ie, such measures should present at least acceptable values of internal consistency based on a Cronbach's alpha coefficient equal or higher than 0.70 and this is reported in the validation study; an overview of the eligible measures of health-related quality of life is presented in table 1); and (5) they used a cross-sectional, case–control or longitudinal design. Studies on chronic LBP associated with radicular pain will be included since the most accepted definitions of LBP also include radicular pain.[3 4] However, studies conducted on radiculopathy

Table 1 Measures of health-related quality of life which will be included in the systematic review

Eligible measures to assess dimensions of quality of life	Evidence about internal consistency reported in the validation study
Medical Outcome Survey Short Form-36 (SF-36)[41]	Values of internal consistency, measured by Cronbach's alpha coefficient, ranged from 0.81 to 0.88 in a sample of 11 186 adult, English-speaking patients who visited physicians (mean age=47 years; 18–103; 38% males)
Quality of Life Inventory (QOLI)[42]	Values of internal consistency coefficients ranged from 0.77 to 0.89 across three clinical and three nonclinical samples
WHOQOL-BREF[43]	In a large sample recruited from five field centres (n=2369), values of internal consistency ranged from 0.70 to 0.86
WHOQOL-100[44]	Values of internal consistency ranged from 0.87 to 0.97 across inpatient, outpatient, primary care and healthy samples

WHOQOL-BREF, World Health Organization's Quality of Life-abbreviated version.

or radicular pain alone without chronic LBP (eg, sciatica, sciatic pain) will be excluded since these conditions are different from chronic non-specific LBP.[4–6] Studies on mixed samples including patients with chronic LBP and radiculopathy will be excluded, unless the data on these two types of conditions are analysed separately. Studies on specific LBP will be excluded. Controls should include individuals recruited from the general population. Trials on the effects of a treatment will be excluded unless they report (or the authors are available to provide them on request) data regarding the requested outcomes at baseline (ie, before trial entry). No language restriction will be applied. Studies will be included whether they used inpatients or outpatients. No restriction on publication dates, languages or country will be used. Studies using patients with a lifetime diagnosis of chronic LBP will not be excluded since chronic back pain is a recurrent disease. Studies where patients had any concurrent psychiatric disorders according to any version of the Diagnostic and Statistical Manual of Mental Disorders (eg, DSM-IV-TR[30] or DSM-5[31]) will not be excluded.

Information sources and search strategy

The search procedure will be conducted on 10th January 2020 for 1 week overall (end of search: 17th January 2020). No restrictions in the search dates and in the languages of the records will be applied. Studies will be identified by conducting a systematic search of electronic databases using Medical Subject Headings (MeSH terms) and keywords related to 'Health-related Quality of Life' which will be combined through the Boolean operator 'AND' with MeSH terms and keywords related to 'Low Chronic Back Pain'. MeSH terms were created through the PubMed MeSH on Demand Tool which allowed us to identify relevant MeSH terms. The search procedure will be conducted using the databases Scopus, PubMed, EMBASE and the Cochrane Library. An overview of the electronic search strategy is provided in table 2.

To identify any further published or unpublished studies, all the authors of the studies included will be contacted. Reference sections of the included studies will be checked. Conference proceedings will be hand-searched from inception for abstracts, papers or posters presented at the following international scientific societies relevant to research on chronic back pain: American Chronic Pain Association, American Psychological Association, British Pain Society, European Association of Neurosurgical Associations and Society for Back Pain Research. This search will be carried out independently by the two reviewers (AP, VFM) by accessing the websites of these scientific societies. Eligible theses and doctoral dissertations will be searched and identified by the two independent reviewers who will run the same queries using the same keywords on the Open Access Theses and Dissertations website. All the searches will be re-run just before the final analyses.

Selection of studies

Studies will be assessed and screened by two independent reviewers (AP, VFM) in three stages using inclusion/exclusion criteria. During the first stage, studies will be assessed independently by the reviewers with regards to inclusion criteria after reading the title. Then, the reviewers will meet to compare their selections. During the abstract selection stage, the two reviewers will independently assess each of the retained studies by reading the abstract and again they will meet to compare their selections. During both these stages (exclusion by title and by abstract), only studies on which both reviewers are in complete agreement on exclusion will be excluded. On the contrary, studies will be retained if there is disagreement between the reviewers on inclusion or exclusion. Studies for which there is complete agreement between the reviewers on inclusion will be included. During the final stage, studies will be assessed independently by the two reviewers by assessing the full text of the paper. Potential discrepancies on inclusion or exclusion at this stage and their reasons will be discussed and resolved in a meeting with two other independent reviewers (FF, AC) to obtain an agreed-upon number of included studies. Between-reviewer agreement on inclusion will be calculated by the Kappa index.[32]

Data extraction

All information will be extracted from each of the included studies by two independent reviewers (AP, VFM) and

Table 2 Electronic search procedure

Electronic databases	Search terms (MeSH and keywords)
Scopus PubMed EMBASE Cochrane Library	MeSH: 'Quality of Life', 'Health-Related Quality of Life' Keywords: HRQOL Health-Related Quality Of Life Life Quality AND MeSH: 'Low Back Pain' Keywords: Low Back Ache Low Back Pain, Mechanical Low Back Pain, Posterior Compartment Low Back Pain, Postural Low Back Pain, Recurrent Low Backache Lower Back Pain Lumbago Mechanical Low Back Pain Postural Low Back Pain Recurrent Low Back Pain OR MeSH: 'Intervertebral Disc Degeneration' Keywords: Degenerative Intervertebral Discs Degenerative Intervertebral Disks Disc Degeneration Disc Degradation Disk Degeneration Disk Degradation Intervertebral Disk Degeneration OR MeSH: 'Intervertebral Disc Displacement' Keywords: Disc, Herniated Disk Prolapse Disk, Herniated Herniated Disc Herniated Disk Intervertebral Disk Displacement Prolapsed Disc Prolapsed Disk Slipped Disc Slipped Disk OR MeSH: 'Sciatica' Keywords: Neuralgia, Sciatic Sciatic Neuralgia Sciatica, Bilateral

MeSH, Medical Subject Heading.

inserted into an Excel (v. 2019) worksheet after an initial pilot extraction using three included studies. Table 3 provides information on what will be extracted and coded

Table 3 Information extracted from the primary studies and coding procedure

Information extracted	Coding
Title of the paper	Full title of the paper
First author name	First author's last name
Publication date	Publication date of the paper
Language of the paper	Language in which the paper is written
Publication on a peer-review journal	'Yes', 'No'
Publication type	'Published on a journal', 'Conference paper', 'Thesis/doctoral dissertation'
Country where the study was conducted	Name of the country
Participants' inclusion criteria	Quote the inclusion criteria reported in the study paper
Participants' exclusion criteria	Quote the exclusion criteria reported in the study paper
Total sample size in the study	
Participants with chronic back pain	Number of clinical participants with chronic back pain
Control participants	Number of control participants
Type of control participants	'Undergraduates', 'Community individuals'
Matched controls	'Yes', 'No'. If Yes, specify if match was made on age or gender or both
Age	Total study mean age and SD
Females	Total percentage of females in the study
Married/cohabitant patients	Total percentage of married/cohabitant patients
Employed patients	Percentage of employed patients
Research design	'Cross-sectional', 'Case–control', 'Longitudinal'
Chronic back pain diagnosis	Diagnostic criteria used to establish diagnosis
Instrument(s) used to establish chronic back pain diagnosis	Acronym of the instrument(s)
Instrument(s) used to assess quality of life	Acronym of the instrument(s)
Type of instrument(s) used to assess quality of life	'Clinician-administered interview', 'Self-report questionnaire'
Age at chronic back pain onset	Mean age at chronic back pain onset in the study
Duration of chronic back pain	Study mean duration of chronic back pain in months
Presence of concurrent psychological treatment	'Yes', 'No'

Continued

Table 3 Continued

Information extracted	Coding
Clinical population	'Outpatient', 'Inpatient'
Strategies used to recruit clinical participants	Quote the strategies reported in the study paper
Strategies used to recruit controls	Quote the strategies reported in the study paper
Setting where clinical participants were recruited	Quote the setting where patients were recruited
Comorbid general medical disease	Percentage of patients with comorbid general medical disease

from the primary studies. A third independent reviewer (FF) not involved in the extraction process will check the correctness of the data inserted in the worksheet. After data insertion is completed, potential discrepancies in the data extracted by the two reviewers will be discussed in a meeting between the reviewers who conducted the data extraction and the third independent reviewer.

Evaluation of study quality

The quality of each study will be independently evaluated using the Newcastle-Ottawa Scale (NOS) for Quality Assessment.[33] This tool assigns a maximum score of 9: 4 points regarding inclusion criteria for cases and controls (definition of cases, selection of cases, definition of controls and selection of controls), 2 points regarding the comparability criteria of cases and controls according to study design and statistical analysis (comparability in terms of age and in terms of gender) and 3 points for exposure verification criteria of cases and controls (exposure verification, same method of verification and no response point). Studies scoring 9 are classified as high quality, those scoring 7 or 8 as medium quality and those scoring less than 7 as low quality. Disagreement in score attribution between the two authors will be settled and resolved by discussion with a third independent reviewer who will be blind to the scores assigned by the other reviewers. Inter-rater reliability between the scores of the scale will be assessed by calculating Cohen's kappa indices.

Meta-Analytic procedure

Summary measures

A random-effect meta-analysis will be conducted using the Comprehensive Meta-Analysis V.2.00 software. For all the analyses, the p-value will be set at 0.05. Random-effect models assume that included studies are drawn from populations of studies that systematically differ from each other.[34] According to these models, effect sizes extracted from included studies differ not only because of random error within studies (as in fixed-effect models), but also because of true variation in effect sizes from one study to another. Summary measures will consist of effect-size indexes related to the levels of health-related quality of life in clinical groups as compared with control groups. Effect-size indexes will be calculated using the following formula proposed by Cohen[35]: $d = (M_{CASE}-M_{CONTROL})/SD_{COMBINED}$, where M_{CASE} and $M_{CONTROL}$ represent the means of the clinical and control groups, respectively, and $SD_{COMBINED}$ is the combined standard deviation. Effect-size indexes will be computed separately from the data obtained from the same scale of the same measure (eg, SF-36 Mental Health Scale).

The score of each index will be weighted using the following correction formula: $W_{zr}=1/SE^2$, where SE^2_{zr} is the standard error of the effect-size index calculated for each study. Using Cohen's model, effect-size indexes greater than or equal to 0.80 are considered high, indexes in the range of 0.80–0.50 moderate and indexes less than or equal to 0.20 low. Hedges' correction for small sample bias will be applied.[36]

During all the phases of the meta-analysis, a close collaboration with a senior statistician (FF) will be requested.

Publication bias

To assess the likelihood that effect sizes have been subjected to publication bias, a visual inspection of the funnel plot will be adopted.[37] A funnel plot is a scatter plot in which the effect sizes computed from the included studies are plotted on the horizontal axis against an indicator of study precision, the SE, on the vertical axis.[37] In the absence of bias, the graph resembles a symmetrical inverted funnel because the effect sizes derived from smaller studies scatter more widely at the bottom of the graph, with the spread narrowing as precision increases among larger studies. If there is publication bias because smaller studies reporting no significant effect sizes remain unpublished, then the funnel plot appears asymmetrical.[37] However, funnel plot asymmetry may also be due to other reasons, including differences in methodological quality (ie, smaller studies tend to be conducted and analysed with less methodological rigour than larger studies), selective outcome analysis or reporting, true heterogeneity (ie, size of effect differs according to study size) and artefactual sources (ie, sampling variation).[38]

As recommended by Sterne *et al*,[38] the Egger test will be computed to test for funnel plot asymmetry. It is an unweighted regression analysis based on the precision of each study as the independent variable and the effect size divided by its SE as the dependent variable. A non-statistically significant result of the t-test for the null hypothesis of an intercept equal to zero, allows to discard publication bias.

Inconsistency analysis

To verify heterogeneity in effect sizes, the I^2 statistic and the Q index will be calculated. The I^2 index is the percentage of variation across studies that is attributable to heterogeneity rather than chance. A value approximating 0 suggests homogeneity, whereas values of 25%–50%, 50%–75% and 75%–100% represent low, moderate and high heterogeneity, respectively. The Q index is calculated

Table 4 Summary of predictors

Predictor	Hypothesis	Rationale and evidence for predictors	Coding
Gender	Total higher percentage of females in the study is associated with larger effect sizes suggesting that female patients report lower health-related quality of life than controls.	Women with musculoskeletal pain report more severe pain, lower quality of life and disability, higher comorbidity levels of psychiatric disorders than men.[25 26]	Total percentage of women included in the study.
Age	Total older age in years in the study is associated with larger effect sizes suggesting that older patients report lower health-related quality of life than the young ones.	Older patients report more severe pain and disability.[27]	Total mean age (in years) in the study.
Comorbidity of psychiatric disorders (mood and/or anxiety disorders)	Percentage of patients with comorbid mood and/or anxiety disorders in the study.	Comorbidity of mood and/or anxiety disorders is higher among patients with chronic LBP than controls and is associated with more severe pain and disability and more dysfunctional coping.[14 15]	Percentage of patients with comorbid mood and/or anxiety disorders in the study according to any version of the DSM: eg, DSM-IV-TR[30] or DSM-5.[31]

DSM, Diagnostic and Statistical Manual of Mental Disorders; LBP, low-back pain.

by summing the squared deviation of each study's effect estimate from the overall effect estimate, while weighting the contribution of each study by its inverse variance. In the hypothesis of homogeneity among effect sizes, the Q statistic follows a χ^2 distribution with k−1 degrees of freedom, k being the number of studies.

Predictor coding and analysis

If inconsistency between effect sizes is found, simple regression analyses by weighted least squares and Analysis of variances (ANOVA) will be performed to investigate whether age and gender can moderate the effect sizes. Gender, age and comorbidity of psychiatric disorders (mood and/or anxiety disorders) will be investigated as moderators of the effect sizes. An overview of the moderators, how they will be coded and the rationale for investigating them is provided in table 4. Following the guidelines for a continuous study-level variable proposed by Fu *et al*,[39] at least 6–10 studies will be necessary to investigate the sources of heterogeneity.

Patient and public involvement

Patients and the public were not involved in the development phase of the research question, the outcome measures and the protocol. The study does not involve patient recruitment and patients were not involved in conduct of the study. The findings will be disseminated through a publication in a peer-reviewed journal.

Ethics and dissemination

The results will be disseminated through publications in peer-reviewed journals.

DISCUSSION AND CONCLUSIONS

Chronic LBP is a leading source of disability worldwide and health-related quality of life is a poorer outcome in patients with this condition compared with healthy individuals. There is a need for a summary of the evidence about this outcome in chronic LBP. In the current literature, there is no systematic review addressing this important topic. The present paper describes a study protocol of the first systematic review whose aim is providing a quantitative summary of the levels of health-related quality of life in patients with chronic non-specific LBP compared with healthy control groups.

Some methodological strengths of the review may be highlighted. First, this systematic review is based on a study selection and a data extraction performed by two independent reviewers; in addition, inter-rater agreement will be evaluated and meeting with other reviewers will be carried out. The use of concurrent psychiatric disorders as exclusion criterion allows us to more clearly investigate the relationship between chronic LBP and health-related quality of life by excluding factors which might distort this association. Any research design will be considered as eligible and this may allow additional data to be located and included even if the focus of the paper is not the comparison of the health-related quality of life levels between patients and controls. Moreover, the search strategy is based on the identification of published and unpublished studies. The search also focuses on data from theses and doctoral dissertations. Lastly, another strength is the evaluation of the study's methodological quality through a specific tool.

The review may have some clinical implications: for example, it can highlight the importance of focusing the

assessment also on quality of life in chronic LBP with the aim to improve prognosis and treatment response.

In addition, a strength will be the analysis of predictors (gender, age and psychiatric comorbidity): the knowledge whether health-related quality of life is better or worse as a function of these variables may suggest personalised care pathways according to a precision medicine approach.[40]

Finally, potential limitations of the review regard a small number of studies in the literature and the heterogeneity of the studies in terms of the instruments used to assess health-related quality of life and the difference in the definitions used to conceptualise this construct. On one hand, the small number of studies may prevent the exploration of the sources of heterogeneity; on the other hand, we can expect that studies are so heterogenous that any meaningful pooling is a difficult step and the case for a narrative review may be a better strategy. Finally, another limitation regards the NOS which does not provide a cut-off.

In conclusion, this is a protocol of the first systematic review of health-related quality of life in patients with chronic LBP. A clearer summary of the evidence on this topic may support clinical practice highlighting the importance of the assessment of quality of life in chronic LBP and suggesting the use of psychological interventions dedicated to this outcome.

Contributors AC designed and conceived the study, critically reviewed the first draft of the paper, will conduct the search, data screening, data extraction and coding. AP designed and conceived the study, conducted the literature searches, wrote the first draft of the paper, will conduct the search, data screening, data extraction and coding. RG designed the study and critically reviewed the first and the final drafts of the paper.GG critically reviewed the final version of the paper. VFM designed and conceived the study, critically reviewed the first draft of the paper, will conduct the search, data screening, data extraction and coding. FF designed and conceived the study, wrote the first draft of the paper, will check data screening, data extraction and coding.

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