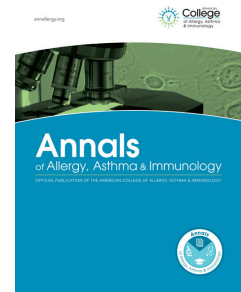


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Psychological functioning and quality of life in patients with mastocytosis: a cross-sectional study.

Running title: Psychological functioning in mastocytosis

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Abbreviations: SF-36: Short Form health survey; SCL-90: Symptom Checklist; WHO: World Health Organization; SM: Systemic Mastocytosis; ISM: Indolent Systemic Mastocytosis; MQLQ: Mastocytosis Quality of Life Questionnaire; SD: Standard Deviation;

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Introduction

Mastocytosis is a chronic hematological disease that is characterized by an accumulation of aberrant mast cells in one or several organs. Symptoms can be caused by tissue infiltration of mast cells or by the excessive release of mast cell mediators such as histamine, eicosanoids, heparin and many different cytokines.¹ In cutaneous mastocytosis, only the skin is involved, whereas systemic mastocytosis is characterized by the involvement of at least one extracutaneous organ, most often the bone marrow.² The WHO has formulated several subtypes of systemic mastocytosis (SM), ranging from indolent to more aggressive forms. When a patient has cutaneous signs of mastocytosis but a bone marrow examination has not been performed, they are termed to have mastocytosis in the skin (MIS).³ Indolent systemic mastocytosis (ISM) is the most common subtype of SM and has virtually no influence on life expectancy.⁴ Nevertheless, it is associated with significant disability – meaning: one or more symptom(s) that prevent the patient from continuing their everyday life. The clinical presentation is very heterogenous and there are various symptoms that negatively impact the quality of life of these patients. From a survey among patients in the USA, the symptoms that were perceived as most debilitating were flushing, diarrhea, fatigue and the everyday risk of anaphylaxis.^{5,6}

Next to these physical symptoms, previous studies have consistently shown an increased prevalence of psychiatric morbidity in patients with mastocytosis.^{7,8} This might be caused by the effect of various mast cell mediators to the brain function.⁷ However, it is still unclear whether psychological morbidity is a specific feature of mastocytosis, or whether it is a more general consequence of having a chronic disease with debilitating physical symptoms. In order to understand the type and extent of psychological symptoms in patients with mastocytosis, it appears useful to make comparisons with emotional and physical distress levels in patients with other diseases. In this study, we therefore aimed to investigate the

presence of various psychological symptoms and quality of life in a representative cohort of patients with mastocytosis and compared these outcomes to already established reference values for patients with chronic pain or cancer and healthy norm groups. Secondly, we analyzed the correlation between psychological symptoms, quality of life and mastocytosis-related characteristics.

Methods

Patients and procedures

A cross-sectional study was performed in 50 adult patients diagnosed with mastocytosis. This study was performed as an addition to a trial that investigated the prevalence and severity of acetylsalicylic acid among adult patients with mastocytosis.¹⁰ Therefore, the inclusion and exclusion criteria were based on that trial. Patients were recruited from the outpatient clinic of a tertiary university medical center, which is a national reference center for mastocytosis.. All patients under current treatment in the fall of 2016 received an invitation to participate by mail and were subsequently contacted by telephone. Adult patients with biopsy-proven cutaneous or systemic mastocytosis were eligible. All participants were asked to complete three questionnaires on psychological symptoms, health-related quality of life and general mastocytosis-related symptoms. The study was approved by the local medical ethics committee. All participants provided written informed consent.

Measures

Basic demographic characteristics and mastocytosis related characteristics such as subtype, presence of skin involvement and anaphylaxis, were recorded. The participants completed the 90-item Symptom Checklist and the 36-item Short Form health survey. These questionnaires were used to screen for psychological symptoms and

health-related quality of life from a patients' perspective. They are not intended to diagnose patients with specific psychiatric diseases.

The Symptom Checklist 90 (SCL-90) is a multidimensional psychopathology-indicator, that assesses to which extent patients were bothered by each item in the last week, including the day of the questionnaire.¹¹ The questionnaire consists of 90 items (symptoms) with scores ranging from 1 (not at all) to 5 (very). There are eight subscales: *anxiety, agoraphobia, depression, somatization, distrust and interpersonal sensitivity, hostility, sleeping problems and inadequacy of thinking and acting*. All items contribute to a total SCL-90 score of psychoneuroticism. Lower scores indicate a better state of recent mental health. Mean test scores of the study cohort were compared to scores of a healthy Dutch norm group and a norm group of patients with chronic pain, described by Arrindell and Ettema.¹¹ The internal consistency of the questionnaire is above 0.70, and most coefficient alpha's range from 0.80 to 1.00.¹¹

The Short Form 36 (SF-36) is a multidimensional measuring instrument that captures the general state of health and functioning, physically as well as emotionally and socially.¹² Item scores are summoned and transformed into eight scale scores: *physical functioning, role limitations due to physical health, role limitations due to emotional problems, vitality, mental health, social role functioning, bodily pain and general health perception*. Overall, a physical health component and mental health component can be discerned. SF-36 outcomes are presented on a hundred-points scale. Higher scores indicate a better state of health. Mean test scores of the study cohort were compared to scores of a healthy Dutch norm group and a norm group of patients with cancer, described by Aaronson et al.¹³ For all test scores the Dutch reference for women was used. The mean coefficient alpha across scales and samples was 0.84.¹³

Lastly, we asked patients to rate 18 mastocytosis-related symptoms in a self-developed questionnaire. These included pruritus, flushing, bone pain, myalgia, dyspepsia, diarrhea, collapse, dizziness, dyspnea, rhinitis, headache, insomnia, fever, night sweats, fatigue, brain fog, subjective cognitive problems, and difficulties with memory. Symptoms were scored from 0 to 3 with 0 meaning 'never present', 1 meaning 'present $\leq$ three days a week', 2 meaning 'present $\geq$ three days a week', 3 meaning 'present every day'.

Analysis

IBM SPSS 25 was used for all analyses. Patient characteristics are given as mean with standard deviation (SD) for continuous variables and as the absolute number with percentage for dichotomous variables. The unequal variances 2-sided t-test was used to compare the mean test scores of the study cohort to norm scores of other populations.^(11, 13) The 2-tailed Pearson correlation coefficient was calculated to investigate a correlation between test scores and continuous variables, and the independent samples t-test was used for dichotomous variables. For all tests α was set at 0.05. A few mastocytosis characteristics that were expected to be correlated to psychological disability, were compared to the main outcomes. These mastocytosis characteristics are tryptase levels, the presence of urticaria pigmentosa and symptoms of fatigue, diarrhea and anaphylaxis. The choice for these characteristics was based on previous literature^{6,14} and our own experience from working with these patients. Test outcomes used for this analysis were: total SCL-90 score and SF-36 mental- and physical health components. By restricting the comparison analyses, a bias due to multiple testing was avoided. Procedures on missing items, provided by Arrindel and Ettema for the SCL-90, and by van der Zee and Sanderman for the SF-36, were followed.^(11, 12) If, according to these guide

lines, not enough items were answered, the patient was excluded from the analysis of the relevant questionnaire.

Results

Patient characteristics

Fifty patients were included. The mean age was 54.3 years (range 19-74 years), the majority of participants was female (68%) and most had indolent systemic mastocytosis (70%). Nine patients (18%) who were under the age of 65 years were not able to work due to health issues. The mean serum tryptase level was 42.5 µg/l, however with a wide range between 6.4 and 221.0 µg/l. The mean duration of disease was 19.2 years, also with a wide range of 2-74 years. Two patients used psychiatric medication, both a selective serotonin reuptake inhibitor. See Table 1 for all patient characteristics.

SCL-90

The study cohort scored significantly higher than the healthy norm group on the total SCL-90 score ($p = 0.02$), but lower than the norm group of chronic pain patients ($p = 0.003$). For the subscales of *depression*, *somatization*, *inadequacy of thinking and acting* and *sleeping problems*, the study population scored significantly worse than the healthy norm group ($p = 0.04$, 0.00002 , 0.002 , 0.001 , respectively), but again lower than the patients with chronic pain ($p = 0.007$, 0.01 , 0.0006 , 0.006 , respectively). There was no significant difference on the subscales of *anxiety*, *agoraphobia* and *interpersonal sensitivity*. See figure 1 for a graphic summary. The exact mean subscale values with standard deviation are summarized in Online Supplementary eTable 1.

SF-36

The study cohort scored significantly worse than the healthy norm group on the subscales of *bodily pain*, *physical role functioning*, *vitality*, *social role functioning*, and *general health perception* ($p = 0.006, 0.001, 0.0002, 0.03, 0.00001$, respectively). There was no difference in the subscales of *mental health*, *emotional role functioning* and *physical functioning* between the study cohort and the healthy norm group. The study cohort scored significantly worse than the norm group of cancer patients on *bodily pain* and similarly on *vitality* and *general health perception* ($p = 0.03, 0.12, 0.64$, respectively). However, cancer patients had significantly lower scores on *mental health*, *emotional role functioning* and *physical role functioning* than our study cohort ($p = 0.0004, 0.008, 0.04$, respectively). See figure 2 for a graphic summary. The exact mean subscale values with standard deviation are summarized in Online Supplementary eTable 2.

Correlation between psychological symptoms and mastocytosis-related characteristics

There was no significant correlation between the serum tryptase levels and the absolute scores of the total SCL-90 and the mental and physical component of the SF-36 (Pearson correlation coefficients 0.128, -0.021, -0.299 with $p = 0.40, 0.90, 0.05$, respectively).

Graphical illustrations are given as Online Supplementary eFigure 1.

The presence of fatigue was significantly correlated with worse scores on the total SCL-90 as well as on the SF-36 mental component and physical component (Pearson correlation coefficients 0.461, -0.380, -0.328 with $p = 0.001, 0.01, 0.03$, respectively). Patients with diarrhea had significantly higher total SCL-90 scores (Pearson correlation coefficient 0.342, $p = 0.02$). Diarrhea was not significantly correlated with worse absolute scores of the SF-36 mental and physical component (Pearson correlation coefficients -0.132, -0.088 with $p = 0.40, 0.56$, respectively). Furthermore, there was no significant correlation between urticaria pigmentosa and the absolute scores of the total SCL-90 and the mental and physical

component of the SF-36 ($p = 0.15, 0.52, 0.26$, respectively). Finally, symptoms of anaphylaxis were not found to be significantly correlated to total SCL-90 scores and the mental and physical component of the SF-36 ($p = 0.08, 0.36, 0.09$, respectively). A graphical illustration of the correlations between these characteristics and the total SCL-90 is given in figure 3.

Discussion

In this cross-sectional cohort study we investigated the presence and type of psychological symptoms of 50 adults with mastocytosis and their health-related quality of life. Secondly, we aimed to identify correlations with mastocytosis-related characteristics. This is the first study to compare psychological symptoms of patients with mastocytosis to historical norm groups of a healthy population and of patients with other illnesses that may greatly impact one's health-related quality of life, i.e. chronic pain or cancer. Patients with mastocytosis scored worse than the healthy norm group on the total SCL-90 scale as well as on its subscales of *depression*, *somatization*, *sleeping problems* and *inadequacy of acting and thinking*. The study cohort scored similar to a healthy norm group on the SF-36 subscales of *mental health* and *emotional role functioning* and similar to a norm group of patients with cancer on the SF-36 subscales of *general health perception* and *vitality* and even worse on the subscale of *bodily pain*.

Previous studies showed that 30-64% of patients with ISM had symptoms of depression^{9,15}, and 38.6% had some degree of cognitive impairment.⁸ In a questionnaire-based cohort study in the USA, 49.3% of patients reported some degree of depression, and 28.8% reported moderate to severe depression.⁶ A similar prevalence of self-reported depression was found

in a Dutch and another French cohort.^{5,16} Since the designs of these studies differ from each other and from the current report, it is difficult to directly compare the results. However, the rates of depression were considerable in every single study. Our study investigated mental and physical burden rather than the presence of specific psychiatric disorders in patients with mastocytosis. For example, the SCL-90 subscale of *depression* is not synonymous to the diagnosis of depression by a psychiatrist. We have used questionnaires that investigate psychological symptoms as well as the health-related quality of life of patients. By comparing our cohort to scores of standard norm groups for the used questionnaires, we can confirm that patients with mastocytosis more often have psychological symptoms than healthy controls. However, our study cohort scored better on most subscales of the SCL-90 than an established norm group with chronic pain. This may not be so surprising, as it is well known that chronic pain is strongly related to psychological functioning.¹⁷ It must be noted that although the use of historical norm groups is in our opinion better than making no comparison at all, it is not certain that these groups are exactly similar to the studied cohort regarding age, sex and other demographic characteristics. Moreover, the norm groups were obtained in the 90's and early 00's, and the general perception of health might have changed with time.

In general, our study population is a representative cohort of adults with mastocytosis, except for a relatively low number of male participants. Only two patients in our cohort were using antidepressants at the moment of obtaining the questionnaires, therefore this is probably not a significant confounder in interpreting the results. On the other hand this low number emphasizes the underestimation of psychological burden in this patient category. Since the researchers work in an allergology-oriented clinic, relatively few patients with advanced subtypes of SM were included. Although the numbers were too small to perform statistical subgroup analyses, the patients with advanced SM did not seem to score worse on the

different questionnaires than patients with MIS or ISM. This might be resultant of the fact that patients with advanced SM usually have less mast cell mediator-related symptoms.¹⁸ Furthermore, only a few study patients had osteoporosis, which can cause chronic pain. The absence of chronic pain due to osteoporosis therefore might have influenced the SF-36 scores in a positive sense. A last possible limitation of our study is the use of self-report questionnaires. This could lead to both under- as overestimation, depending on the coping style of the included patients.

Strikingly, patients with mastocytosis have a similar perception of their general health to patients with cancer. The fact that 18% of the studied patients were not able to work due to their mastocytosis-related health issues stresses the debilitating nature of this disease in everyday life. Other studies that investigated the quality of life of patients with mastocytosis reported that both fatigue as well as the unpredictability of symptoms such as anaphylaxis, diarrhea and flushing have a large influence on their quality of life.^{14,19} Our results indeed showed positive correlations between fatigue, the total SCL-90 and the mental and physical component of the SF-36. Furthermore, the presence of diarrhea was significantly correlated to the total SCL-90 score. Correlations with serum tryptase levels, anaphylaxis and urticaria pigmentosa did not prove significant.

It appears logical that experiencing these debilitating symptoms on a daily basis negatively influences one's perception of overall health and can result in a depressed mood. Accordingly, other studies found a high prevalence of clinically significant fatigue among patients with mastocytosis, ranging from 43.4% to 62.4%.^{6,20,21} Several phenomena could contribute to the increased perception of fatigue in patients with mastocytosis. Firstly, depressive symptoms often coincide with a feeling of fatigue.²² Secondly, fatigue in the

presence of chronic disease could also be explained in the context of the sickness behavior response. This is an automated response, triggered by innate immunity activation, to increase the survival of an animal by decreasing their activity.²³ However, as mastocytosis patients continuously have high levels of various mast cell mediators, this might exert direct effects on the brain. Recent research indeed showed an impaired tryptophan metabolism in patients with mastocytosis.⁷ A small cohort study also showed a high prevalence of atypical white matter lesions in patients with mastocytosis (49%) and an increased perfusion of the putamen region compared with healthy controls.⁹ The fact that treatment with the tyrosine kinase inhibitor masitinib has a positive effect on psychological symptoms suggests that depression may indeed be an endogenous manifestation of mastocytosis, rather than a sole secondary consequence of physical illness.¹⁵

On a final note, this study was not designed to identify biological pathophysiological processes that cause psychological symptoms in mastocytosis. For future studies, it would be interesting to combine all aspects mentioned above: neurobiological processes, the patient's own perspective, and the evaluation by an expert mental health professional.

In conclusion, patients with mastocytosis score higher on psychological symptoms when compared to healthy controls, but lower than patients with chronic pain or cancer. More specifically, patients with mastocytosis significantly more often have depressive symptoms, sleeping problems, somatic complaints and inadequacy of acting and thinking, compared to healthy controls. Strikingly, patients with mastocytosis score similar to cancer patients on the SF-36 subscale of general health perception. These findings stress the importance of correct treatment of physical mastocytosis-related symptoms, as well as adequate psychological counselling for patients with mastocytosis.

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Legends to figures

Figure 1. Mean SCL-90 subscale scores of the study cohort compared to norm scores of healthy persons and patients with chronic pain. A higher score means more symptoms. The y-axis depicts the absolute mean score value. On the x-axis, the subscales of the Dutch SCL-90 subscales are shown. Anx = anxiety; Ago = agoraphobic symptoms; Dep = depression; Som = somatization; In = inadequacy of thinking and acting; Sen = interpersonal sensitivity; Hos = hostility; Sle = sleeping problems.

* $p < 0.05$ for comparison of the subscale value of the study population versus the healthy norm group (t-test)

Figure 2. Mean SF-36 subscale values of the study cohort compared to SF-36 norm scores of the Dutch population and cancer patients. A lower score means lower quality of life on that area. The y-axis depicts the absolute score value. The subscales on the x-axis are shown as abbreviations of the SF-36 subscales. BP = bodily pain; PF = physical functioning; RP = physical role functioning; RE = emotional role functioning; VT = vitality; MH = mental health; SF = social role functioning; GH = general health perception.

* $p < 0.05$ for comparison of the subscale value of the study population versus the healthy norm group (t-test)

$p < 0.05$ for significantly worst subscale score for the study population versus the norm group of cancer patients (t-test)

Figure 3. Graphical illustration of the association between the total SCL-90 score and **A**) fatigue ($p = 0.001$), **B**) diarrhea ($p = 0.017$), **C**) urticaria pigmentosa ($p = 0.15$) and **D**) anaphylaxis ($p = 0.08$). Symptoms were scored by the patients themselves and rated from 0 to 3 with 0 meaning 'never present', 1 meaning 'present $\leq$ three days a week', 2 meaning 'present $\geq$ three days a week', 3 meaning 'present every day'.

Table 1. Baseline characteristics study population (n=50).	
Age in years, mean (SD)	54.3 (12.8)
Male, n (%)	16 (32)
Educational level, n (%)	
• High school	2 (4)
• Secondary vocational education	27 (54)
• Higher professional education	16 (32)
• University education	5 (10)
Currently working‡, n (%)	28 (56)
• Not working due to health issues	9 (18)
• Retired	12 (24)
Subtype according to WHO criteria ^{2, 15} , n (%)	
• MIS	9 (18) [§]
• ISM	
with skin lesions	26 (52)
without skin lesions	9 (18)
• SSM	3 (6)
• SM-AHN	2 (4)
• ASM	1 (2)
Duration of disease in years, mean (SD)	19.2 (14.4)
Serum tryptase level at diagnosis in µg/l, mean (SD)	42.5 (47.8)
Daily mast cell mediator-related symptoms, n (%)	
• Pruritus	36 (72)
• Flushing	35 (70)
• Diarrhea	36 (72)
• Fatigue	43 (86)
• Anaphylaxis	22 (44)
• Osteoporosis†	8 (16)
MIS: mastocytosis in the skin; ISM: indolent systemic mastocytosis; SSM: smouldering systemic mastocytosis; SM-AHN: systemic mastocytosis with associated hematological neoplasm; ASM: aggressive systemic mastocytosis. [§]One patient underwent incomplete bone marrow investigation, 8 patients declined bone marrow puncture. †Osteoporosis was defined as a T-score $\leq$ 2.5 SD for bone densitometry of the lumbar spine and/or left femur. ‡One person is a housewife.	

Figure 1. Mean SCL-90 subscale scores of the study cohort compared to norm scores of healthy persons and patients with chronic pain.

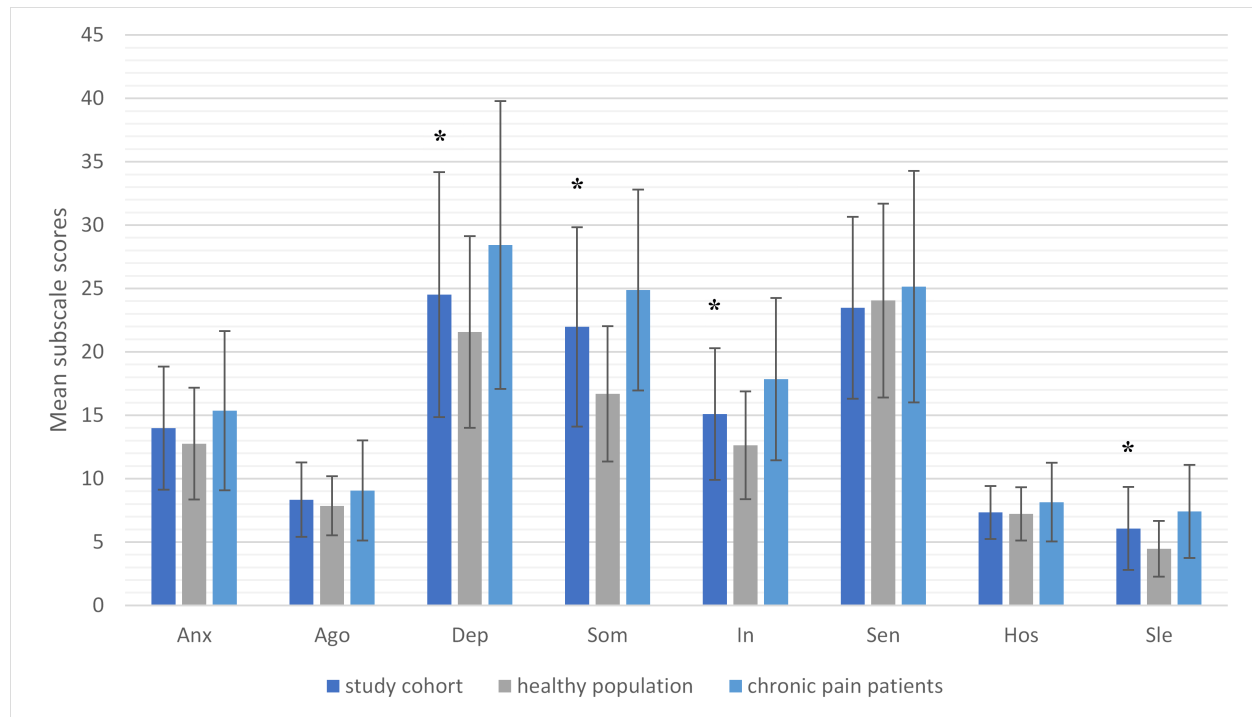


Figure 2. Mean SF-36 subscale values of the study cohort compared to SF-36 norm scores of the Dutch population and cancer patients.

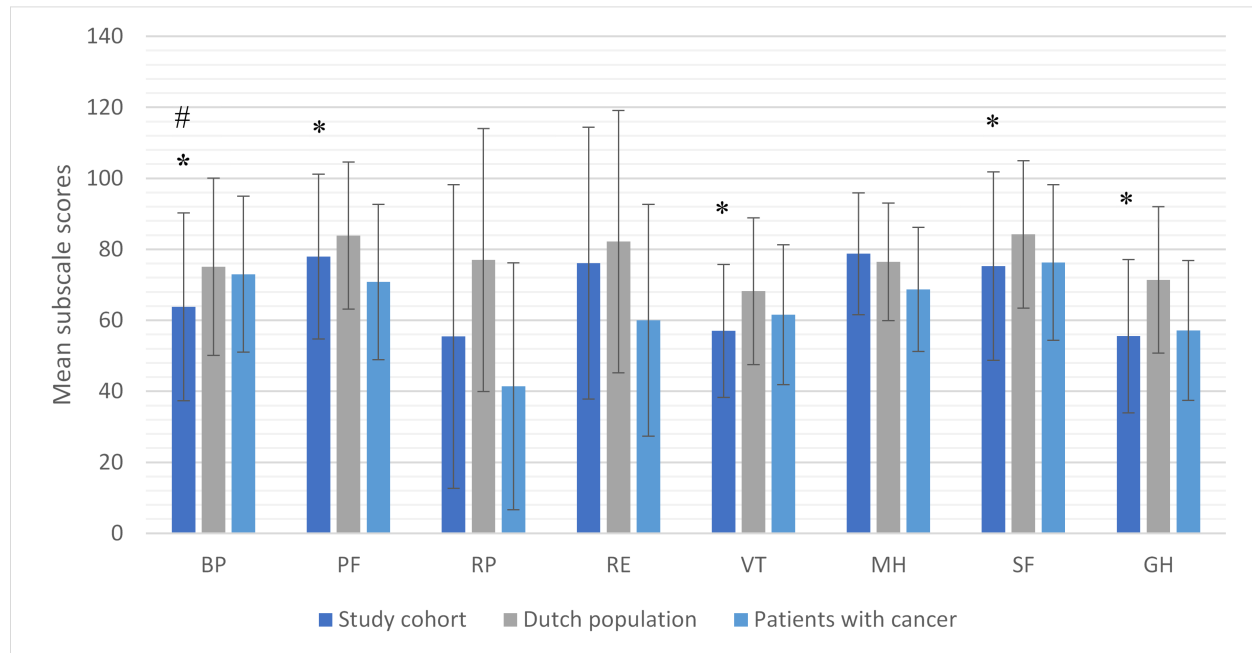


Figure 3. Graphical illustration of the association between the total SCL-90 score and a) fatigue (p 0.001), b) diarrhea (p 0.017), c) urticaria pigmentosa (p 0.15) and d) anaphylaxis (p 0.08).

