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**Patient-reported outcomes and their relation with iron parameters in HFE  
haemochromatosis during maintenance therapy:**

**A prospective cohort study**

**Short title:** *Patient-reported outcomes and iron parameters in haemochromatosis*

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**Abbreviations:** BMI: body mass index - PRO: Patient- Reported Outcomes - QoL: Quality Of Life - SF-36: Short Form 36 Health Survey - TS: Transferrin Saturation.

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**Keywords:** Haemochromatosis; HFE; quality of life; patient-reported outcomes; transferrin saturation

**Ethics:** The study protocol was approved by the ethics committee of Rennes (n° 16-146, December 2016). All patients provided written informed consent.

**Data availability statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Summary**

**BACKGROUND & AIMS:** The standard of care of hemochromatosis is regular phlebotomy in order to maintain low ferritin levels. Many patients report fatigue or joint pain despite serum ferritin within the therapeutic targets. We evaluated Patient-Reported Outcomes, and their relation with iron parameters, in C282Y homozygous patients undergoing maintenance phlebotomy.

**METHODS:** Patients were prospectively enrolled in a French referral care centre. At each phlebotomy, patients completed a numeric fatigue scale, a joint pain questionnaire, and SF-36

Mental Component Score (MCS) and Physical Component Score (PCS). Hemoglobin, iron, TS and ferritin were collected concomitantly.

RESULTS: 701 visits were performed in 259 patients. The median fatigue score was 3/10; 171 (66%) patients reported joint pain. Age and worsening of joint pain were associated with fatigue ( $P < .0001$  for both). Female gender ( $P < .037$ ), age ( $P < .003$ ), and a decrease of TS ( $P = .050$ ) were associated with joint pain. Main features associated with PCS  $< 50$  were worsening of joint pain and age ( $P < .001$  for both) and TS  $< 20\%$  ( $P < .02$ ).

CONCLUSIONS:

Fatigue was independent from iron parameters. The main factor impacting quality of life was joint pain, which was more severe in patients with low TS values. Then, a more precise monitoring of TS should be proposed during hemochromatosis maintenance therapy; while less stringent monitoring of serum ferritin levels could be tested.

**Lay Summary/Key points:**

- A significant proportion of hemochromatosis patients treated with phlebotomy as maintenance therapy reports joint pain and fatigue, despite serum ferritin within the therapeutic targets.
- In this prospective cohort of 259 hemochromatosis patients, 50% of patients reported a significant fatigue level, and 2/3 reported joint pain. Joint pain worsening and low TS levels were associated with impaired quality of life, while no association was found between patient-reported outcomes and ferritin levels.
- Then, a more precise monitoring of transferrin saturation should be proposed for the management of hemochromatosis patients under maintenance therapy, while less stringent monitoring of serum ferritin levels could be tested.

## **Introduction**

The homozygous C282Y mutation of the HFE gene is the most common aetiology of hemochromatosis. Homozygosity for the p.C282Y variant in HFE is associated with increased plasma iron and transferrin saturation, which is the biological hallmark of the disease.<sup>1</sup>

Phlebotomy is the standard of care for hemochromatosis. Current recommendations for phlebotomy regimen are based on biological parameters: American guidelines recommend maintaining serum ferritin levels between 50 and 100 µg/L, whereas European recommendations suggest maintaining ferritin levels under 50 µg/L.<sup>2-4</sup> Hence, phlebotomy regimen is not established depending on patients functional symptoms, especially fatigue and joint pain. Yet, many patients experience poor quality of life (QoL) in maintenance therapy even if the ferritin level target has been achieved.

Among the various symptoms that are reported by hemochromatosis patients, fatigue and joint pain are two major determinants of QoL.<sup>5</sup> However, few studies have evaluated patient-reported outcomes (PRO), especially fatigue and joint pain, and their relation with iron parameters, in hemochromatosis patients in maintenance therapy. PRO use, including quality of life assessment, is currently widely encouraged for chronic diseases management, as it has been found an efficient way to improve patients' health.<sup>6,7</sup>

Therefore, we designed the present prospective cohort study in order to evaluate fatigue, joint pain and QoL, and to search for an association of these outcomes with iron parameters, in a large cohort of C282Y homozygotes patients under maintenance therapy, with the final objective to optimize patient's phlebotomy regimen, in a patient-centred care perspective.

## **Materials and Methods**

### *Study Design*

We conducted a prospective study in the liver unit of Rennes University Hospital, France, a referral tertiary care centre. The study protocol was approved by the ethics committee of Rennes (n° 16-146, December 2016) and was registered in Clinical Trial Gov (NCT number: 03356548). All patients provided written informed consent.

### *Subjects*

Between April 2017 and April 2019, hemochromatosis patients undergoing regular phlebotomy in our centre for maintenance therapy were included if they were aged 18 years or more and if they were under maintenance therapy for at least 6 months. The study visit was

postponed for patients with signs of infections (fever, diarrhoea, urinary tract or ENT symptoms) in the past 7 days. During this period, hemochromatosis patients completed self-administrated questionnaires at each phlebotomy-visit as part of their routine maintenance therapy. Serum iron parameters were also measured at each visit. Patients were blinded from the results of serum iron parameters.

### *Study objective*

The primary objective was to assess the association between patients fatigue and joint pain, and iron parameters.

### *Data collection*

At each phlebotomy, study participants completed self-administered questionnaires. The first questionnaire focused on patients' habitus: current occupation, consumption of alcohol, tea and coffee as well as medications intake. The second questionnaire was devoted to auto-evaluation of fatigue. As no specific fatigue-assessment instrument is validated in hemochromatosis patients, we used a numeric scale derived from the Piper fatigue scale, which was previously validated in the general French population.<sup>8,9</sup> Patients reported the intensity of fatigue felt in the past three days, ranging from 0: no fatigue, to 10: strong fatigue. According to Piper et al, a fatigue score  $\geq 7$  defined a severe fatigue.<sup>10</sup> To assess the association between fatigue and other parameters, fatigue was either considered as a continuous or as a dichotomic variable ( $\leq$  vs  $>$  of the median value in our population). The third questionnaire was the medical outcomes study 36-item short-form health survey (SF-36), which has already been used in hemochromatosis patients, including a Physical Component Score (PCS) and a Mental Component Score (MCS).<sup>11,12</sup> For SF-36, the threshold of 50 was considered to define altered QoL since this threshold is the normative score of the general population.<sup>13</sup> A third questionnaire focused on joint symptoms; since no instrument was available for the evaluation of musculoskeletal outcomes in hemochromatosis patients, we designed a questionnaire including the following items: i) presence of joint pain in hands, wrists, elbows, shoulders, knees, ankles (Yes/No), and ii) worsening of joint pain during the previous week before study visit, which was assessed by the following question: "Have you experienced a worsening of your joint pain over the previous week?". This question aimed to capture potential flare up of

hemochromatosis related joint pain at the end of phlebotomy interval. The variable resulting from this item was labelled “worsening of joint pain” for subsequent analyses.

A pilot version of the questionnaires was administered to a panel of 5 hemochromatosis patients prior to study initiation, and was modified according to their comments to ensure intelligibility and relevance of question phrasing.

All questionnaires were repeated at each phlebotomy during the study period. Weight, height, and waist circumference, were measured by clinical nurses at the first study visit. Abdominal obesity was defined by a waist circumference > 40 inches (102 cm) in men and >35 inches (88 cm) in women. Obesity was defined by a BMI >30 kg/m<sup>2</sup>. Date, time and volumes of phlebotomy were collected. The concentration of ferritin and transferrin saturation in serum, and the concentration of hemoglobin in blood, were determined in a non-fasting blood sample taken at the beginning of each phlebotomy.

#### *Statistical analysis*

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Qualitative variables are presented with numbers and percentages. Quantitative variables are expressed with mean±SD. Qualitative data associations were analysed conducting Chi-square test or Fisher’s exact test. Data were analysed conducting the Student’s t-test or Mann Whitney U test depending on Gaussian distribution. Receiver operating characteristic curves were used to determine the most discriminant cutoffs for fatigue.

Uni- and multivariate models were used to test the associations between study parameters and fatigue, low MCS, low PCS, presence of joint pain and worsening of joint pain. Covariates including gender, age at first visit, professional activity, proton pump inhibitors intake, prescribed psychopharmacological treatment, joint pain, worsening of joint pain, BMI, abdominal obesity, TS, ferritin, tea and excessive alcohol consumption and hemoglobin level were included in multivariate models.

Uni- and multivariate analyses were adjusted on follow-up duration and study visits, and were conducted using a generalized linear mixed model with repeated measures to leverage all measurements during study follow-up. With this method, correlations among repeated measures can be modelled by specifying a covariance structure, to control for iterative bias. All tests were two-tailed, with a significance level of  $P < .05$ .



## Results

Among the 259 included patients, 205 completed 3 visits, 41 had only 2 visits and 13 had only 1 visit, with a total of 710 visits recorded in the study database. Mean follow-up during the study was  $6 \pm 2.6$  months.

### *Characteristics of the patients*

Mean age was  $57.2 \pm 12.3$  years, 13 (5%) patients were over 75 years-old, 152 (58.7%) were men. Mean body mass index was  $25.3 \pm 4.1$  kg/m<sup>2</sup>. Mean time from diagnosis of hemochromatosis to study entry, that is the duration since when patients were on phlebotomy treatment, was  $15.7 \pm 9.0$  years. Only 17 patients had liver fibrosis grade 3 or 4. Excessive alcohol consumption (i.e., > 20 g/day for women and >30 g/day for men) was found in 8 (7.5%) women and in 16 (10.5%) men. Daily consumption of 3 cups or more of coffee or tea was reported in 37.5% and 13.0% of patients, respectively. One hundred and forty-seven (57%) patients were engaged in an occupational activity. Forty-five patients (17.5%) were taking a prescribed psychopharmacological treatment.

### *Biological features*

At the time of diagnosis, mean ferritin level was  $1040 \pm 1135$  µg/L. Amount of iron removed was  $5.03 \pm 4.3$ g. Mean MR hepatic iron concentration was  $200 \pm 88$  µmol/g (available in 127/259 patients).

Mean serum ferritin at study entry was  $48 \pm 43$  µg/L and mean TS was  $46 \pm 19\%$ . Overall, a ferritin > 50 µg/L was observed in 211 (29.7%) visits. A TS below 20% (normal range 20-40%) in at least one visit was observed in 28 patients. There were significant intra-individual variations of TS between visits (mean variation of  $8.9 \pm 46.4\%$ ,  $p=0.003$ , between visit 1 and 2; and mean variation of  $11.6 \pm 54.2\%$ ,  $p=0.003$ , between visit 1 and 3).

### *Analyses of fatigue-related questionnaires*

Mean fatigue level based on the Piper-derived scale was  $3.7 \pm 2.5$ . Thirty-two (12.4%) patients had no fatigue (scale score of 0) and 46 (17.8%) had severe fatigue (scale score of 7 to 10). There were significant intra-individual variations of fatigue levels among visits (mean variation of  $25.1 \pm 95.0\%$ ,  $p<0.0001$ , between visit 1 and 2; mean variation of  $25.8 \pm 89.4\%$ ,  $p<0.0001$ , between visit 1 and 3). Median value for fatigue was 3. Mean SF-36 MCS was  $46.3 \pm 9.9$ , and

mean PCS was  $49.5 \pm 8.5$ . Regarding the question “In general, would you say your health is...” from SF-36, 62 (23.9%) patients reported that they feel their health excellent or very good, 165 (63.7%) good and 32 (12.4%) fair or bad.

#### *Analyses of pain-related questionnaires*

Regarding the question “How much bodily pain have you had during the past 4 weeks?” from SF-36, 114 (44.9%) reported none or very mild, 126 (49.6%) mild or moderate and 14 (5.5%) severe or very severe. One hundred and seventy-one (66%) patients reported the presence of at least one joint pain (most frequent were knees ( $n=101$ , 39%) and hands ( $n=85$ , 32.8%)) while 41 (15.8%) patients disclosed a worsening of their joint pain during the week before phlebotomy.

#### *Features associated with fatigue*

Fatigue score was correlated with MCS ( $r = -0.59$ ;  $P < .001$ ) and with PCS ( $-0.28$ ;  $P < .001$ ) components of the SF-36, but not with TS. After ROC curves analysis, the most discriminant cut-off value for fatigue was  $>3$ , which also corresponded to the median value in our population. Patients with fatigue score  $>3$  were significantly younger ( $P < .009$ ) and more frequently were engaged in an occupational activity ( $P < .0001$ ). They also had phlebotomy performed at a later time of the day ( $P < .001$ ). Moreover, they more frequently reported joint pain ( $P < .0001$ ) and prescribed psychopharmacological treatment ( $p = 0.004$ ). Mean SF-36 PCS and MCS components were significantly lower in patients with fatigue score  $>3$  ( $P = .0001$ ). There was no association between fatigue and TS or ferritin (Table 1).

In multivariate analysis, worsening of joint pain was associated with fatigue (OR=4.77;  $P < .0001$ ). Age was also associated with a fatigue score  $>3$  (OR, 0.96;  $P < .0001$ ), meaning a 0.96-fold decrease in the risk of disclosing a fatigue  $>3$  for each additional year of age. There was no association between fatigue and TS, neither as a categorial variable ( $<20$  vs  $>20\%$ ) nor as a continuous variable (Table 4).

#### *Features associated with joint symptoms*

Patients reporting joint pain were more frequently woman ( $P < .0003$ ), were older ( $P < .0001$ ), had lower SF-36 PCS ( $P < .0001$ ) and had more frequently ferritin  $<50$  ( $P = 0.05$ ). A significant association was found between reported joint pain and TS diminution, both as a continuous variable and with the threshold of 20% ( $P = .001$  and  $P = .025$ , respectively). Higher daily tea and alcohol consumption were also found in these patients (Table 2). In multivariate

analysis, female gender and age were associated with the presence of joint pain. An association between TS and joint pain was found (OR, 0.992;  $P = .050$ ) meaning a 0.08% decrease of the risk of having joint pain for a one-point elevation of TS (Table 4).

Worsening of joint pain during the week before phlebotomy was associated with ferritin  $<50$  ( $P = .022$ ), and low TS as a continuous variable ( $P = .006$ ) or with  $TS < 20\%$  ( $P = .002$ ). Patients reporting a worsening of their joint pain also had lower PCS and MCS ( $P < .0001$ ), and reported higher tea consumption ( $P = .046$ ) (Table 3).

In multivariate analysis, only proton pump inhibitors intake was significant, and there was also no association with TS (Table 4).

#### *Features associated with SF-36 PCS and MCS*

Patients with  $PCS < 50$  were more frequently women ( $P = .007$ ), were older ( $P = .002$ ), had a lower TS ( $P = .002$ ) and more frequently a  $TS < 20\%$  ( $P = .006$ ). They also showed a more frequent excessive abdominal obesity ( $P = .0007$ ), alcohol consumption ( $P = .014$ ), and psychoactive drugs intake ( $P = .011$ ). They more frequently reported joint pain ( $P < .0001$ ) and a worsening of their joint pain ( $P < .0001$ ), and had a lower MCS ( $P < .0001$ ). In multivariate analysis, worsening of joint pain, age, abdominal obesity, and  $TS < 20\%$ , were associated with  $PCS < 50$  (Table 4).

Patients with  $MCS < 50$  were younger ( $P = .0008$ ), had a lower ferritin level ( $P = .023$ ), a higher coffee consumption ( $P = .003$ ). They were more frequently receiving psychoactive drugs ( $P < .0001$ ). They reported more frequently a worsening of their joint pain ( $P < .0001$ ). In multivariate analysis, worsening of joint pain and anti-depressant treatment intake were associated with  $MCS < 50$ , while age was associated with a better MCS (Table 4).

## **Discussion**

This study evaluated the association between patient-reported outcomes, including quality of life, fatigue and joint pain, and iron parameters values, in a cohort of C282Y homozygotes patients undergoing maintenance therapy. Firstly, we observed significant intra-individual variations of PRO and iron parameters between study visits, demonstrating the

interest of the statistical global linear mixed model with repeated measures that was used, allowing us to leverage the repeated measures that were carried out in the successive visits.

Secondly, two thirds of patients reported joint pain, mainly in the hands and knees, during their follow-up. Such high prevalence of joint pain was previously reported by Richette et al,<sup>14</sup> who observed 50.5% of arthropathy in a French population of hemochromatosis with a mean age of 60 years, and by Sahinbegovic et al,<sup>15</sup> who reported 72.4% of joint pain in German middle-aged hemochromatosis patients. In the present study, multivariate analysis found age, female gender, and TS as factors associated with joint pain. The greater frequency of arthralgia with age may be explained by the increasing incidence of global bodily pain and osteoarthritis with age, as previously described in general population.<sup>16</sup> Nonetheless, even if our questionnaires were not specifically designed to discriminate haemochromatosis related joint pain from other non- hemochromatosis specific joint manifestations, the preferential localization of pains in hands and knees in our patients argued in favor of their relation with hemochromatosis.<sup>14,15,17</sup> Female gender is not clearly reported in the literature as a risk factor for joint pain in hemochromatosis. However, in a study which compared the symptoms present in women with those of men in hemochromatosis patients, arthralgia were reported in 45% of women versus 35% of men, while another study found female gender to be associated with hemochromatosis osteoarthritis.<sup>18,19</sup> Still, we cannot rule out a potential confounding role of osteoporosis, as osteodensitometry examinations were not performed. The most intriguing finding is that a decrease in TS, studied as a continuous variable, was associated with an increased risk of joint pain. This association was independent of BMI, whereas high BMI can both promote joint pain and lower TS.<sup>20</sup> As C-reactive protein was not measured in our study, we cannot exclude that this association reflected an inflammatory joint process, such as hemochromatosis related calcium pyrophosphate deposition disease (pseudogout), leading to a drop in TS.<sup>21</sup> Finally, even if there was no difference regarding blood volume removed between patients with TS<20 and those with TS>20, a deleterious effect of excessive blood volume removal *per se* cannot be excluded, since the effect of bleeding has already been reported as being able to worsen joint pain in hemochromatosis.<sup>22,23</sup> These results are not concordant with a previous work conducted by our group, in which an association between an exposure longer than 6 years to increased TS and an aggravation of joint pain was observed, in a longitudinal study of patients treated for hemochromatosis.<sup>24</sup> However, in that study patients retrospectively reported their symptoms since initiation of maintenance therapy, meaning a mean period of  $13.5 \pm 5.9$  years, and iron parameters were not measured simultaneously. Moreover, as TS

values were used as an AUC, this study did not permit to consider specifically patients with low TS values.

Fatigue is frequently reported among hemochromatosis patients, with a detrimental impact on QoL.<sup>5,25</sup> Nonetheless, no specific questionnaires has been validated in hemochromatosis population. This symptom is difficult to assess as it is highly subjective and includes both physical and emotional dimensions.<sup>26</sup> Hence, we chose to use a simple numerical scale derived from the Piper questionnaire<sup>8,9</sup> to evaluate fatigue in a quantitative approach. Physical and mental components of SF-36 questionnaire also assessed overall QoL. In our study, we found worsening of joint pain as being the factor the most strongly associated with fatigue, as well as with lower SF-36 PCS and MCS. In accordance with a previous study conducted in general Norwegian population, we found age increase to be associated with better MCS and fatigue assessed by the Piper score, while the influence on PCS was negative.<sup>16</sup> This could be explained as only 13 patients were >75, while the majority of older subjects in our population were "young retirees", and many studies have shown the beneficial effect of retirement on mental health, which could be explained by the reduction of work-related stress.<sup>27</sup> Conversely, taking psychoactive treatments was associated with a poorer MCS-score. An association between hemoglobin level and fatigue was found in univariate analysis, but it was inconsistent between study visits, did not seem clinically relevant, and was not found significant in multivariate analysis. Abdominal obesity, and TS below 20% were independently associated with a lower PCS, possibly through joint manifestations, as shown by the association between TS decrease and the presence of joint pain. Nonetheless, it should be noted that only 28 patients had TS<20% at least one time over the study period. Finally, the absence of association between fatigue and elevated TS challenges the direct link between this symptom and hemochromatosis. In line with this, Pilling et al showed that the risk of frequent tiredness was not different between C282Y homozygotes and heterozygotes or normal controls in a large UK cohort.<sup>28</sup>

Finally, we didn't find any relation between ferritin and either the presence or the intensity of fatigue, and joint pain, confirming previous reports of the absence of correlation between iron load and symptoms.<sup>25</sup> We also evaluated the effect of baseline iron overload on study outcomes, and the inclusion into the analysis of either ferritin at diagnosis, or the amount of iron removed during the induction phase, did not change the study results.

The main limitation of our study is that it was conducted in a single, tertiary care centre. To our knowledge, no other study has aimed to prospectively evaluate PRO and their relation with iron parameters so far, in the specific setting of hemochromatosis patients undergoing maintenance therapy. Therefore, our findings would need to be validated in an independent cohort.

A second limitation of our study is that iron parameters were not measured in a fasting state, as there is a diurnal variation in the iron cycle.<sup>29</sup> However, in current practice, measurements are made at the time of phlebotomy, as guidelines do not recommend fasting samples. Moreover, the measurements were always made at the same time of the day for each patient in our study.

Regarding TS, only significant associations were found between, on one hand, TS as a continuous variable and the presence of joint pain, and on the other hand, between TS <20 and PCS<50. Although TS<20 is particularly low, and not routinely used in clinical practice, this threshold corresponded to the lower limit of the normal range of TS for males in our laboratory (20-45%). This association between TS<20 and PCS<50 was not confirmed when categorizing TS in quartiles. Hence, as the small number of patients exhibiting a TS<20 may have limited our results, further studies focusing on patients with low TS will be needed to explore in depth the effect of low TS on patients' quality of life, and to confirm this low TS threshold effect.

In conclusion, two thirds of hemochromatosis patients under maintenance therapy reported joint pain, which was the main factor of alteration of quality of life, as evidenced by its impact on both physical and psychological components of SF-36. These symptoms were independent of ferritin levels and were more severe in patients with TS<20%. Then, a more precise monitoring of TS should be proposed during the follow-up of hemochromatosis patients under maintenance therapy, while a less strict monitoring of ferritin could be tested. A prospective randomized trial testing this strategy is needed.

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Fatigue Level Variable	Visit 1			Overall
	0-3 (n=137)	4-10 (n=122)	p	p
Gender (n/%) female	50(36.5)	57(46.7)		
male	87(63.5)	65(53.3)	0.08	<b>0.026</b>
Age at diagnosis (years)	42.9(11.1)	39.8(11.5)	0.45	<b>0.009</b>
Age at first visit (years)	59.7(11.1)	54.5(13.1)	0.007	<b>0.0001</b>
Blood volume removed (ml/kg)	5(1.1)	4.9(1.1)	0.32	0.15
Time of blood sampling (hh:mm)	11.58(2.56)	13.10(2.52)	0.009	<b>0.0001</b>
Haemoglobin (g/dL)	14.4(1.07)	14.2(1.1)	0.14	<b>0.018</b>
Ferritin (ug/L)	50.2(43.2)	45.6(42)	0.53	0.37
Ferritin (n/%) ≤50 (ug/L)	90(65.7)	94(77)		
>50 (ug/L)	47(34.3)	28(23)	0.67	0.12
TS (%)	47.3(18.8)	44.9(18.8)	0.98	0.42
TS (n/%) 00-20 %	5(3.7)	9(7.4)		
21-92 %	132(96.3)	113(92.6)	0.71	0.40
BMI (kg/m <sup>2</sup> )	25.6(4.1)	25(4.1)	1	0.27
Tea consumption ≥3 cups/d	19(14.3)	14(11.6)	0.38	0.37
Coffee consumption ≥3 cups/d	52(38)	45(37)	0.52	0.40
Excessive alcohol consumption	15(11)	9(7.4)	0.42	0.92
Professional activity no	67(49.3)	44(36)		
yes	69(50.7)	78(64)	0.004	<b>0.0001</b>
Psychopharmacological treatment	15(11)	30(24.6)	0.12	<b>0.004</b>
Joint pain no	55(40.2)	33(27)		
yes	82(59.8)	89(73)	0.017	<b>0.0001</b>
Number of painful joints	3.19(0.6)	3.71(1.1)	0.0001	<b>0.0001</b>
Worsening of joint pain no	131(95.6)	87(71.3)		
yes	6(4.4)	35(28.7)	0	<b>0.0001</b>

SF36: PCS	51.2(6.7)	47.6(9.9)	0.001	<b>0.0001</b>
SF36: MCS	50.7(7.3)	41.2(10.1)	0.0001	<b>0.0001</b>

Table 1. Univariate analysis of features associated with fatigue level, at first study visit and overall.

Qualitative variables are expressed in numbers/%; quantitative variables are expressed in mean ( $\pm$ SD) unless otherwise indicated. Blood volume removed is expressed in ml/kg. “p-overall” was obtained with linear mixed models with repeated measures to control for iterative bias.

Table 2. Features associated with the presence of joint pain, at first study visit and overall.

		Visit 1			Overall
Joint pain		No	Yes	p	p
Variable		(n=88)	(n=171)		
Gender	female	28(31.8)	79(46.2)	0.09	<b>0.0003</b>
	male	60(68.2)	92(53.8)		
Age at diagnosis (years)		39.2(11.1)	42.6(11.4)	0.001	<b>0.0001</b>
Age at first visit (years)		53.9(12.7)	58.9(11.8)	0.001	<b>0.0001</b>
Blood volume removed (ml/kg)		5(1.1)	4.9(1.1)	0.57	0.74
Time of blood sampling (hh: mm)		12.46(3.07)	12.25(2.53)	0.12	0.14
Haemoglobin(g/dL)		14.4(1.07)	14.2(1.1)	0.14	<b>0.018</b>
Ferritin level (ug/L)		49.1(27.7)	47.5(48.6)	0.64	0.54
Ferritin level (n/%)	≤50	56(63.6)	128(74.9)	0.24	<b>0.05</b>
	>50	32(36.4)	43(25.1)		
TS (%)		48.6(18.6)	44.8(18.9)	0.048	<b>0.001</b>
TS (n/%)	00-20	3(3.4)	11(6.4)	0.13	<b>0.025</b>
	21-92	85(96.6)	160(93.6)		
BMI (kg/m <sup>2</sup> )		24.6(3.6)	25.7(4.3)	0.29	0.08
Tea consumption ≥3 cups/d		6(6.9)	27(16.17)	0.037	<b>0.005</b>
Coffee consumption ≥3 cups/d		26(29.55)	71(41.52)	0.06	0.3
Excessive alcohol consumption		5(5.68)	19(11.18)	0.15	0.015
Professional activity	no	32(36.36)	79(46.47)	0.13	0.012
	yes	56(63.64)	91(53.53)		
Psychopharmacological treatment		14(15.9)	31(18.1)	0.47	0.85
SF36: PCS		54.1(6.2)	47.2(8.6)	0.001	<b>0.0001</b>
SF36: MCS		46.7(9.2)	46.(10.3)	0.48	0.18

Qualitative variables are expressed in numbers/%; quantitative variables are expressed in mean ( $\pm$ SD) unless otherwise indicated. Blood volume removed is expressed in ml/kg. “p-overall” was obtained with linear mixed models with repeated measures to control for iterative bias.

Table 3. Univariate analysis of features associated with the worsening of joint pain during the week before study visit, at first study visit and overall.

Worsening of joint pain Variable	Visit 1			Overall
	No (n=218)	Yes (n=41)	p	p
Gender (n/%)				
f	88(40.4)	19(46.3)		
m	130(59.6)	22(53.7)	0.018	<b>0.006</b>
Age at diagnosis (years)	41.5(11.3)	41.1(12)	0.041	0.13
Age at first visit (years)	57.3(12.4)	57.2(12.1)	0.3	0.39
Blood volume removed (ml/kg)	5(1.1)	4.6(1)	0.58	0.18
Time of blood sampling (hh:mm)	12.36(3.01)	12.10(2.36)	0.41	0.4
Haemoglobin (mg/dL)	4.98(1.11)	4.59(0.96)	0.048	<b>0.018</b>
Ferritin level (ug/L)	48(37.9)	48.2(62.5)	0.98	<b>0.06</b>
Ferritin level (n/%)<=50	152(69.7)	32(78)		
>50	66(30.3)	9(22)	0.12	<b>0.022</b>
TS (%)	47(18.5)	41.6(20.3)	0.21	<b>0.006</b>
TS (n/%)				
00-20	8(3.7)	6(14.6)		
21-92	210(96.3)	35(85.4)	0.009	<b>0.002</b>
BMI (kg/m <sup>2</sup> )	25.2(4)	26.1(4.6)	0.34	0.13
Tea consumption ≥3 cups/d	25(11.74)	8(19.51)	0.18	<b>0.046</b>
Coffee consumption ≥3 cups/d	81(37.16)	16(39.02)	0.82	0.58
Excessive alcohol consumption	19(8.76)	5(12.2)	0.49	0.62
Professional activity				
no	93(42.9)	18(43.9)		
yes	124(57.1)	23(56.1)	0.87	0.56
Psychopharmacological treatment	32(14.7)	13(31.7)	0.5	0.17
SF36: PCS	50.4(7.9)	44.4(10.1)	0.001	<b>0.0001</b>
SF36: MCS	47.1(9.8)	41.6(9.4)	0.0001	<b>0.0001</b>



Qualitative variables are expressed in numbers/%; quantitative variables are expressed in mean ( $\pm$ SD) unless otherwise indicated. Blood volume removed is expressed in ml/kg. “p-overall” was obtained with linear mixed models with repeated measures to control for iterative bias.

Table 4. Significant associations between patients' characteristics and fatigue, PCS, MCS and joint pain, in multivariate analysis including all study visits.

	OR [IC95]	N=259	P-value
<b>Fatigue &gt;3</b>			
Worsening of joint pain during the week before study visit	4.77 [3.09-7.38]	41	<0.0001
Age	0.96 [0.95-0.98]	259	<0.0001
<b>PCS&lt;50</b>			
Worsening of joint pain during the week before study visit	2.56 [1.72-3.81]	41	<0.0001
Age	1.03 [1.01-1.05]	259	0.001
Excessive waist circumference	1.85 [1.18-2.90]	92	0.03
Missing	1.24 [0.93-1.67]	13	
<b>TS &lt;20%</b>	2.11 [1.10-4.03]	14	0.02
<b>MCS&lt;50</b>			
Worsening of joint pain during the week before study visit	2.15 [1.39-3.32]	41	0.0006
Age	0.97 [0.96-0.99]	259	0.004
Psychopharmacological treatment	2.37 [1.36-4.12]	45	0.002
<b>Presence of joint pain</b>			
Female gender	1.67 [1.03-2.69]	107	0.037
Age	1.03 [1.01-1.05]	259	0.003
<b>TS (continuous)</b>	0.992 [0.984-1.000]	259	0.050
<b>Worsening of joint pain</b>			
Gastric protective medication intake	2.20 [1.11-4.38]	24	0.025

The following variables were included in the multivariate model: *gender, age at first visit, professional activity, proton pump inhibitors intake, psychotropic medications, joint pain, worsening of joint pain, BMI, abdominal obesity, TS, ferritin, tea and alcohol consumption and haemoglobin level.*