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**Pain rate and social circumstances rather than cumulative organ damage determine the quality of life in adults with sickle cell disease.**

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3 1 **Due to the significant morbidity associated with sickle cell disease (SCD) sickle cell**  
4 **patients have a reduced quality of life (QoL). Even though pain is considered an**  
5 **important determinant of QoL in sickle cell patients, factors such as organ damage and**  
6 **socioeconomic circumstances may also be important. Therefore we determined the**  
7 **contribution of chronic organ damage and sickle cell related complications to QoL and**  
8 **also analysed the effect of vaso-occlusive crises and socio-economic circumstances on**  
9 **QoL. Consecutive adult sickle cell patients were included. QoL was represented in a**  
10 **physical component scale (PCS) and a mental component scale (MCS) and assessed with**  
11 **SF-36 forms. Higher pain rates were related to lower QoL scores. Both occupation and**  
12 **the level of education were significantly related to PCS while no relation with MCS or**  
13 **pain rate was found. Thirty-five percent patients were unemployed as compared to 6%**  
14 **of the general population and 16% of immigrants without SCD. Neither genotype nor**  
15 **the presence of chronic organ damage were significantly related to QoL. In conclusion, a**  
16 **reduced QoL was mainly determined by pain rate, occupation and educational level.**  
17 **Chronic organ damage, although a major factor determining life expectancy in SCD,**  
18 **was not a determinant of QoL.**

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Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by recurrent microvascular vaso-occlusion and chronic hemolytic anemia resulting in progressive organ damage and reduced life expectancy. [1;2] Given the chronic nature of SCD and the severity of its complications, patients are likely to have a significantly reduced quality of life (QoL). Intuitively and historically, pain is widely regarded as the major factor in determining QoL in SCD. However, even though previous studies have indeed demonstrated a reduced QoL of sickle cell patients, this was often not or not only attributable to pain. [2] Factors such as anxiety, depression and socioeconomic circumstances may also contribute to the reduced QoL of sickle cell patients. [3-5]

Sickle cell patients develop organ damage irrespective of their frequency of acute painful events which has been related to significant morbidity and increased mortality and it seems likely that SCD related organ damage negatively impacts QoL of sickle cell patients. [6] However, to our knowledge, the impact of chronic organ damage on QoL in SCD has not been previously assessed. Therefore, we prospectively assessed the QoL in a cohort of consecutive sickle cell patients in whom chronic organ damage, pain rate and the history of sickle cell related complications in the last five years was systematically analyzed. In addition, the impact of occupation and educational level on QoL of these patients was studied.

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3 35 117 adult patients with sickle cell disease (HbSS, HbS $\beta^0$ :HBSC, HbS $\beta^+$ ) were eligible  
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5 36 for our study. Twenty-three patients were excluded from analysis because they were not able  
6  
7 37 to fill in the SF-36 questionnaire for different reasons (illiterate persons, mental retardation or  
8  
9 38 repeated no show at their appointments). These excluded patients did not differ from the study  
10  
11 39 population concerning outcome variables (pain, disease severity, education and occupation).  
12  
13 40 QoL was assessed in 51 patients with HbSS, 5 with HbS $\beta^0$ , 11 with HbS $\beta^+$  and 27 patients  
14  
15 41 with HbSC.

16 42 The QoL data of our population are presented in table I. As expected, our patient  
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18 43 group scored lower on QoL compared to the healthy Dutch population [9] (data not shown).  
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20 44 No correlation between the MCS and PCS was found in the sickle cell population (spearman  
21  
22 45  $r=0.14$ ;  $P>0.20$ ). When comparing male to female sickle cell patients the overall PCS  
23  
24 46 appeared to be significantly higher in males as compared to females ( $P=0.015$ ). We found no  
25  
26 47 significant difference in the overall MCS between males and females. Older patients scored  
27  
28 48 lower on the PCS in comparison to younger patients ( $P=0.002$ ) while no significant  
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30 49 differences in QoL scores between genotypes was found (data not shown).

31 50 The QoL scores in relation to pain rate are depicted in table II. With respect to the  
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33 51 MCS, the overall score and all subscales, except for mental health, were significantly lower in  
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35 52 patients with the highest pain rate ( $P=0.021$ ). Although significantly lower scores were found  
36  
37 53 on the role-physical (RF) scale ( $P=0.005$ ) and the general health (GH) scale ( $P=0.033$ ) in  
38  
39 54 patients with the highest pain rate the overall PCS was not determined by the number of  
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41 55 admissions for painful crises ( $P=0.110$ ). Also analysis by linear regression confirmed that  
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43 56 pain rate is significantly associated with MCS and is less likely to influence the PCS (data not  
44  
45 57 shown).

46 58 The prevalence of different forms of organ damage in our study population was: PHT:  
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48 59 24,5%, renal failure: 3,2%, microalbuminuria: 21,3%, retinopathy: 31,2%, iron overload:  
49  
50 60 9,6%, avascular osteonecrosis: 11,7% leg ulcers: 6,4%, ACS: 25,5%, priapism: 8,5% and  
51  
52 61 stroke: 4,3%. Except from lower QoL scores (for the PCS) in patients with iron overload  
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54 62 ( $p=0.017$ ), no association between any form of organ damage or sickle cell related  
55  
56 63 complications and QoL scores was found (table III). Moreover, when patients with organ  
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58 64 damage and complication were divided according the pathogenesis (hemolysis related  
59  
60 65 complication versus vaso-occlusion/ischemia related complications) no significant differences  
61  
62 66 in QoL was observed as compared to the patients without organ damage at all.

63 67 With respect to the relation between occupation and educational level and QoL scores,  
64  
65 68 the PCS was strongly associated with occupation and level of education ( $p<0.001$ ). The

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3 69 overall MCS was not related to occupation or the level of education (respectively  $p=0.206$  and  
4 70  $p=0.177$ ). Occupation and the level of education were not different between different  
5 71 genotypes and were not related to pain rates.

6 72 Sickle cell disease (SCD) is heterogeneous in its clinical presentation with patients  
7 73 being continuously admitted for the management of disease related complications at one end  
8 74 of the spectrum, and patients rarely requiring medical care at the other. [6] Irrespective of the  
9 75 frequency of acute clinical complications, most patients develop accumulating organ damage  
10 76 throughout their lives as result of chronic hemolytic anemia and ongoing vaso-occlusion. [1]  
11 77 With respect to QoL, previous studies have reported that sickle cell patients have lower QoL  
12 78 scores as compared to race and age matched controls which were related to pain. [18-20]  
13 79 However, its relation to the presence of chronic organ damage has not been described before.  
14 80 In the present study organ damage appeared not to be related to any of the QoL scores. If  
15 81 patients were grouped according the pathophysiology of their different forms of organ  
16 82 damage or a history of sickle cell related complication as recently proposed by Kato et al.,  
17 83 also no relation with QoL scores was demonstrated. [15] Surprisingly, PHT, which has been  
18 84 related to early mortality in SCD, was not related to QoL in our patients. This might be  
19 85 explained by the fact that our study population consists of patients with mild PHT  
20 86 (regurgitation jet flow velocity  $< 2.9$  m/s) which is generally not related to severe complaints  
21 87 or significantly reduced exercise tolerance.

22 88 Factors significantly associated with a reduced QoL were pain rate and social  
23 89 circumstances defined as educational level and occupation. Interestingly, pain rate was only  
24 90 associated with a reduced MCS while the social circumstances of the patients were related to  
25 91 the PCS. These data suggest that frequent painful and unpredictable crises are an important  
26 92 psychological burden rather than a physical burden to sickle cell patients as has been  
27 93 suggested previously. [21] In contrast, social circumstances as reflected by occupation and  
28 94 level of education were mainly related to the PCS, suggesting that only patients in good  
29 95 physical performance are able to finish school and find jobs independently of the frequency of  
30 96 admission for painful crises. This was further supported by the finding that no correlation  
31 97 between the MCS and PCS was found in the sickle cell population, which is in contrast to the  
32 98 findings of QoL assessments in healthy individuals. [9] Similar to previous findings of  
33 99 McClish et al. we did not find a correlation between genotype and QoL scores. [20] Also no  
34 100 difference in QoL scores was observed between patients on hydroxyurea and those who are  
35 101 not on hydroxyurea. This might be explained by the fact that in our study population  
36 102 hydroxyurea was only prescribed to reduce painful crises and the occurrence of acute chest

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3 103 syndrome. By reducing these complications in patients with an otherwise more severe clinical  
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5 104 presentation, hydroxyurea may have improved the QoL. This is in line with a previous  
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7 105 prospective study of Ballas et al. who demonstrated an improved QoL with the use  
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9 106 hydroxyurea.[22]

10  
11 107 Certain limitations of our study should be taken into account. First, by defining pain  
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13 108 rate by the amount of clinical admissions, the conclusions of our study may not be  
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15 109 extrapolated for the number of painful crises experienced at home which have been reported  
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17 110 to occur frequently in sickle cell patients. [23] However, previous studies have shown that  
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19 111 pain (during a painful crises as well as chronic pain) is related to QoL in sickle cell patients.  
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21 112 [18;20;22] Second, most forms of organ damage and sickle cell related complications were  
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23 113 only present in a relative small group of patients which may have underpowered our study to  
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25 114 detect an effect of specific forms of organ damage on QoL. Mild pulmonary hypertension, as  
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27 115 one of the most relevant forms of organ damage which has been associated with poor  
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29 116 prognosis, was present in 24% of all sickle cell patients and was not related to QoL.

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31 117 In conclusion, the quality of life scores in consecutive sickle cell patients appear to be  
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33 118 determined mainly by pain rate and social circumstances. Despite the contribution of organ  
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35 119 damage such as (mild) pulmonary hypertension on prognosis and life expectancy, cumulative  
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37 120 organ damage does not seem to be an important determinant of QoL in SCD. In terms of  
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39 121 clinical presentation, pain rate is the most important factor for the QoL of adult sickle cell  
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41 122 patients.

### 42 123 **Methods**

43  
44 124 Adult sickle cell patients visiting the Department of Hematology of the Academic  
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46 125 Medical Centre (AMC) in Amsterdam were eligible for our study. Inclusion criteria were:  
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48 126 high performance liquid chromatography (HPLC) confirmed diagnosis of homozygous sickle  
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50 127 cell anemia (HbSS), sickle-C disease (HbSC), HbS $\beta^+$ -thalassemia (HbS $\beta^+$ -thal) or HbS $\beta^0$ -  
51  
52 128 thalassemia (HbS $\beta^0$ -thal), age 18 years or older and capable of filling in a questionnaire  
53  
54 129 (Dutch or English). All data were collected during a routine outpatient clinic visit.

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56 130 QoL was assessed by the use of SF-36 forms. The SF-36 is a short-form health survey  
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58 131 which has been proven to be valid and reliable in het black population. [7] It has been  
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60 132 previously used to determine QoL in adults with SCD. [8] Briefly, it yields eight different  
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134 133 scales (physical functioning, role limitations due to physical problems, role limitations due to  
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136 134 emotional problems, social functioning, mental health, vitality, bodily pain and general health  
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136 135 perceptions) of functional health and well-being as well as psychometrically-based physical  
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136 136 and mental health summary measures. The SF-36 is a generic measure, which is not age,



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3 137 disease or treatment specific. Accordingly, the SF-36 has proven to be useful in surveys of  
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5 138 general and specific populations, comparing the relative burden of diseases. [9] All patients  
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7 139 were asked to complete this questionnaire during a routine out-patient visit. All scale scores  
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9 140 are linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of  
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11 141 functioning or well being. We analyzed the scores of our study population and compared the  
12  
13 142 data with the scores of the general healthy Dutch population. [9]

14 143 Data on social circumstances represented by occupation and level of education were  
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16 144 routinely gathered during the first routine visit for every patient. With respect to occupation  
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18 145 patients were divided in: employed, unemployed or student. Education level was divided in:  
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20 146 high school or less, vocational education/ community college and tertiary education/university.

21 147 Pain rate was defined as the number of admissions for treatment of a vaso-occlusive  
22  
23 148 crisis from January 2002 until January 2007 and was determined by chart review. [6]  
24  
25 149 Subsequently three groups were arbitrarily defined: patients without, patients with < 1  
26  
27 150 admission for painful crises per year and patients with 1 or >1 admission for painful crisis  
28  
29 151 per year.

30 152 Organ damage and sickle cell related complications were assessed by systematic  
31  
32 153 screening and medical record review and defined as follows: *Pulmonary hypertension (PHT)*:  
33  
34 154 tricuspid regurgitation jet flow velocity (TRV) equal to or higher than 2.5 m/sec in rest  
35  
36 155 detected by Doppler echocardiography. PHT was considered absent with no or only trace  
37  
38 156 TRV. [10] *Renal failure*: an estimated creatinine clearance lower than 100 mL/min  
39  
40 157 (Cockcroft and Gault). *Microalbuminuria*: urinary creatinine (mmol/L) to urinary albumin  
41  
42 158 (mg/L) ratio higher than 3.5 for males and higher than 2.5 for females confirmed with 24  
43  
44 159 hours urine collection with microalbuminuria higher than 30 mg/24 hours. [11] *Retinopathy*:  
45  
46 160 presence of at least mild non-proliferative retinopathy. [12] *Iron overload*: plasma ferritin  
47  
48 161 level higher than 1000  $\mu\text{mol/L}$  (on at least three occasions during steady state) and a history  
49  
50 162 of more than 20 transfused packed cells. [13] *Symptomatic avascular osteonecrosis*: local  
51  
52 163 pain and reduced function with documented osteonecrosis of the femoral or humeral head (hip  
53  
54 164 or shoulder X-ray) or a history of surgical intervention for osteonecrosis. *Leg ulcers*: chronic  
55  
56 165 ulcers of the ankle not otherwise explained. *Acute chest syndrome*: defined as described by  
57  
58 166 Stuart et al. occurring between January 2002 and January 2007. [14] *Priapism*: spontaneous  
59  
60 167 painful erection requiring hospital care. *Stroke*: history of stroke confirmed by magnetic  
168  
169 168 resonance imaging or computerized tomography. We analyzed the relation between organ  
170  
170 169 damage and QoL both for each form of organ damage or complication separate as well as for  
170  
170 169 groups. Groups were divided in a group with no organ damage or sickle cell related

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3 171 complications, a group with organ damage or complications due to hemolysis (leg ulcers,  
4 172 PHT, priapism and stroke) or a group with organ damage related to vaso-occlusion (ACS,  
5 173 retinopathy, avascular osteonecrosis, renal failure and microalbuminuria) as proposed  
6  
7 174 previously. [15]

8  
9 175 Hematological and biochemical laboratory parameters were assessed at the same visit  
10 176 at which the patient completed the QoL questionnaire. Fetal hemoglobin percentage (HbF%)  
11 177 was determined by cation-exchange high performance liquid chromatography and  $\alpha$ -  
12 178 thalassemia screening was performed with a multiplex PCR assay. [16] If not available we  
13 179 used the results from the latest outpatient visit. [17]

14 180 All numbers in the tables are medians with corresponding inter quartile ranges (IQR)  
15 181 unless stated otherwise. Difference in continuous data between groups was tested with the  
16 182 Mann-Whitney test. Difference in categorical data between groups was tested with the Chi-  
17 183 square test. P-values  $\leq 0.05$  were considered statistically significant. Multiple linear regression  
18 184 analyses were performed to analyze the interaction between the different scales of the SF-36  
19 185 questionnaire and pain rate. All missing data were considered missing at random. In the case  
20 186 that one or more questions were not answered in a specific scale of the SF-36 questionnaire,  
21 187 the mean value of the remaining questions on that specific scale was used for the missing  
22 188 items. When half or more of the questions were not answered, the results of the specific scale  
23 189 were discarded. Statistical analysis was performed by using SPSS 12.0.2 (SPSS Inc, Chicago,  
24 190 IL).



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**Table I. QoL scores of sickle cell patients**

	Male	Female	
	SCD N=32	SCD N=61	P*
PCS	42.5 (10.9)	36.9 (11.9)	0.000
Physical Function	72.5 (24.2)	57.4 (28.0)	0.000
Role-Physical	54.8 (43.5)	43.8 (43.6)	0.000
Bodily Pain	60.8 (27.4)	50.5 (28.5)	0.000
General Health	48.3 (23.3)	41.0 (23.1)	0.000
MCS	48.4 (12.6)	43.9 (12.1)	0.023
Vitality	59.5 (20.8)	45.4 (19.3)	0.000
Social Function	73.8 (25.3)	62.7 (28.4)	0.000
Role-Emotional	70.0 (41.4)	57.2 (45.1)	0.035
Mental Health	74.0 (21.3)	63.6 (21.3)	0.000

Mean (SD)

\* Mann-Whitney-test

**Table II. QoL in relation to pain rate**

	<b>None (n=25)</b>	<b>&gt;0&lt;1 (n=48)</b>	<b>&gt;=1 (n=21)</b>	<b>P*</b>
PCS	45.3 (34.4-52.1)	39.6 (29.5-49.3)	33.4 (28.8-39.2)	0.110
Physical Function	70.0 (35.0-90.0)	70.0 (45.0-90.0)	60.0 (39.7-75.0)	0.390
Role-Physical	87.5 (0.0-100.0)	50.0 (0.0-100.0)	0.00 (0.00-50.0)	0.005
Bodily Pain	62.0 (36.5-92.0)	52.0 (32.0-80.0)	41.0 (26.5-61.0)	0.102
General Health	52.0 (30.0-83.3)	37.0 (25.0-57.0)	39.5 (21.3-47.0)	0.033
MCS	50.6 (39.3-57.6)	50.8 (38.3-57.1)	36.7 (30.4-48.2)	0.021
Vitality	55.0 (37.5-75.0)	50.0 (43.8-65.4)	40.0 (31.3-48.8)	0.022
Social Function	75.0 (56.3-100.0)	75.0 (50.0-100.0)	50.0 (37.5-75.0)	0.003
Role-Emotional	100.0 (8.3-100.0)	100.0 (33.3-100.0)	0.00 (0.00-100.0)	0.032
Mental Health	80.0 (46.0-92.0)	72.0 (48.0-89.0)	56.0 (52.0-68.0)	0.319

Median (IQR)

\*Kruskal Wallis Test

**Table III. QoL in relation to organ damage and sickle cell related complications.**

Manifestations	N	PCS		P*	MCS		P*
		Present	Absent		Present	Absent	
Pulmonary hypertension	23	39.8 (11.3)	38.5 (11.6)	0.701	50.2 (10.3)	44.3 (12.8)	0.060
Renal failure	3	28.4 (14.4)	39.0 (11.4)	0.132	50.3 (11.1)	45.2 (12.4)	0.466
Microalbuminury	20	34.9 (10.5)	39.9 (11.9)	0.106	41.6 (13.6)	46.6 (12.3)	0.186
Retinopathy	30	37.4 (10.6)	38.6 (11.9)	0.638	47.5 (11.6)	45.5 (12.4)	0.463
Iron overload	9	30.1 (8.3)	39.9 (11.8)	0.017	41.4 (12.4)	45.9 (12.4)	0.348
Avascular osteonecrosis	11	36.1 (7.7)	39.0 (12.1)	0.444	39.8 (13.8)	46.1 (12.0)	0.449
Leg ulcers	6	38.5 (11.9)	38.6 (11.7)	0.966	40.6 (7.3)	45.6 (12.5)	0.344
Acute chest syndrome	24	35.0 (12.9)	40.1 (11.2)	0.057	46.3 (10.6)	45.2 (13.0)	0.843
Priapism	8	45.7 (7.8)	41.4 (11.8)	0.425	47.4 (11.1)	48.7 (13.4)	0.606
Stroke	4	42.2 (13.0)	38.7 (11.8)	0.190	45.7 (16.9)	45.5 (12.3)	0.429

Mean (SD)

\* Mann Whitney U Test