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Are serum hsCRP and IL-6 prognostic markers in somatic symptom disorder and related disorders? An exploratory analysis in a prospective cohort study

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ABSTRACT

Objective: To investigate the roles of hsCRP and IL-6 as prognostic markers for treatment outcome in SSRD.
Methods: In this prospective cohort study, 237 consecutive outpatients diagnosed with SSRD at the Clinical Centre of Excellence for Body Mind and Health, the Netherlands were assessed. At intake, venepuncture was performed for serum hsCRP and IL-6. Baseline scores for PHQ-9, GAD7, physical symptom score (PSQ-51) and BPI questionnaires were obtained. Patients were followed up at the end of their usual treatment programme, which lasted approximately 12 months.
Results: Higher baseline hsCRP was associated with high physical symptom scores (PSQ-51), but not BPI, GAD-7 and PHQ-9 questionnaire scores at end of treatment. No association was identified between baseline IL-6 and follow-up symptom questionnaire scores after treatment. Adjustment for age, gender and somatic comorbidity showed no significant change in the association.
Conclusion: This exploratory analysis provides some evidence that in patients with SSRD, high baseline serum hsCRP may predict poorer treatment outcomes in physical symptoms but not depression, anxiety or pain symptoms. Baseline serum hsCRP may therefore be a useful factor in identifying SSRD patients who are at risk of a persistent high physical symptom burden.

1. Introduction

DSM-5 Somatic symptom disorder and related disorders (SSRD) affect approximately 5–7% of the population. They are characterised by at least six months of somatic symptoms accompanied by distress, expressed by excessive thoughts, feelings and/or behaviours in response to these somatic symptoms. These conditions include, amongst others, somatic symptom disorder (SSD), conversion disorder or functional neurological disorder (CD/FND), and illness anxiety disorder [American Psychiatric Association 2013]. The pathophysiology remains poorly understood. In general, it is presumed to involve a combination of biological, psychological and social factors, that can be aggravated by interactions with health care professionals and health services [Ratcliff, J & Van Der Feltz-Cornelis, CM. 2020]. In this article we focus on a possible biological explanation, which may involve chronic systemic low-grade-inflammation (SLI) [Ratcliff, J & Van Der Feltz-Cornelis, CM. 2020].

In SLI, at the molecular level, neuroinflammatory and systemic cytokines such as interleukin-6 (IL-6), and high sensitivity C-reactive protein (hsCRP) are thought to play a role [Van Der Feltz-Cornelis, CM et al., 2020].

Macrophages secrete IL-6 in the acute phase, which binds to hepatocytes to increase C-reactive-protein (CRP) production. In the adaptive phase IL-6 plays a role in activating antibody-producing B-Cells [Tanaka, T et al., 2014]. Several studies have identified an association between IL-6 and mental illness [Chase KA et al., 2016; Ting EY et al., 2020]. Life stressors have been shown to lead to a surge in IL-6, which hyper-methylates regulatory genes for Brain-Derived-Neurotropic-Factor

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(BDNF). This leads to reduced BDNF expression [Foran E et al., 2010], which has been seen to reduce neuronal growth and connectivity. This state has been associated with impaired memory, somatic pain, and depressive, anxiety and physical symptoms [Bath and Lee, 2006]; which occur often in SSRD. This epigenetic process has been implicated in pathogenesis of several psychiatric disorders including non-epileptic attack disorder [Dincheva I et al., 2016; Youssef MM et al., 2018; LaFrance WC et al., 2010].

CRP is produced by hepatocytes and binds to dying cells and some bacteria to promote phagocytosis [Bodman-Smith KB et al., 2002]. It plays a key role in innate immunity, however its role in mental illness remains poorly understood. CRP places a crucial role in the activation of the complement system via the classical pathway that involves component-3a (C3a) and complement-component-5a (C5a), which act as potent chemokines to basophils, mast cells, neutrophils, T-cells and macrophages. Subsequent mast cell and basophil degranulation leads to local vasodilation, increased vascular permeability, pain sensitization, cell apoptosis and smooth muscle contraction, which are characteristic features of inflammation [Merle NS et al., 2015]. Furthermore, C3a and C5a have been implicated as important regulators of synaptic pruning, neural plasticity and neuronal migration during development. Indeed, dysregulation of the complement system and high C3a and C5a have been associated with neurological and psychiatric diseases, such as neuropathic pain, chronic pain and schizophrenia [Druart, M., & Le Magueresse, C. 2019].

Fig. 1 illustrates the theoretical roles of hsCRP and IL-6 in SSRD pathogenesis.

Although these inflammatory processes have been associated with symptoms that also occur in SSRD, such as pain and fatigue [Bath and Lee, 2006; Druart, M., & Le Magueresse, C. 2019], their pathogenic role in SSRD remains uncertain.

In terms of clinical applications, CRP is currently used as non-specific marker for inflammation, as it is elevated in infection, cancer and autoimmune conditions [Mayo Clinic, 2020]. CRP has been associated with a variety of mental illnesses, particularly with regards to depression where it may act as a marker for treatment resistance [Chamberlain SR et al., 2019]. Patients who remain in a chronic state of SLI, with a CRP of between 3 and 10 mg/l, show an increased risk of developing type 2 diabetes mellitus, cardiovascular complications and mental illness [Cozlea DL et al., 2013; Kanmani S et al., 2019; Myung W et al., 2016; Tayefi, M et al., 2017]. Traditional testing measures CRP between 10 and 100 mg/l, however high-sensitivity-CRP testing (hsCRP) is able to measure CRP between 0.5 and 10 mg/l [Chamberlain SR et al., 2019]. Numerous studies have identified that hsCRP is able to act as a prognostic marker in cardiovascular disease and the American Heart Association advocate the use of hsCRP to stratify risk of cardiovascular disease in individuals over 50 [Adukauskienė, D et al., 2016; Pearson TA et al., 2003]. Furthermore, patients with an elevated hsCRP show better response to certain statins and immunotherapies in the prevention of cardiovascular disease [Ridker PM et al., 2017; Ridker, P. M. et al., 2009]. With regards to mental health, immunotherapy is proving to have promising potential in the treatment of depression, anxiety, schizophrenia and bipolar disorder [Akhondzadeh S. 2019; Miller, B. J., & Buckley, P. F. 2016; Rosenblat JD et al., 2016]. This raises the question of a potential role of hsCRP in personalised medicine in psychiatry.

No other studies have sought to investigate the roles of inflammatory markers in symptom profiling to predict the prognosis in SSRD – an asset that would prove valuable in tailoring treatment, understanding pathophysiology and stratifying treatment based on SLI risk in SSRD patients [Van der Feltz-Cornelis CM. 2020].

1.1. Aim

We therefore aimed to explore the relationship between baseline serum hsCRP and IL-6 on physical symptoms, anxiety, depression, an pain in SSRD patients after treatment.

To do this we conducted a novel exploratory analyses of data from a prospective cohort study of 237 participants with a diagnosis of SSRD.

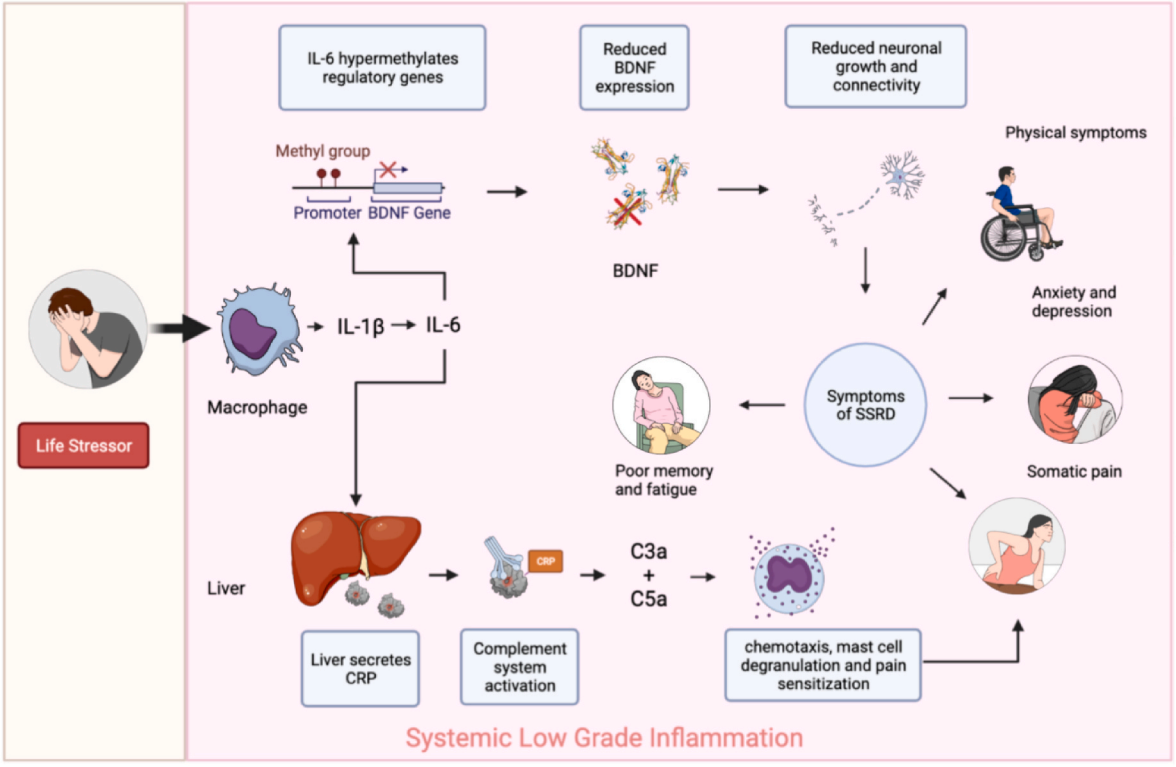

Fig. 1. Possible roles of SLI in SSRD pathogenesis.

2. Material and methods

In this prospective cohort study, 237 consecutive patients diagnosed with SSRD at the Clinical Centre of Excellence for Body Mind and Health (CLGG) in GGz Breburg, a specialty mental health clinic in Tilburg, the Netherlands, which is a last resort for complex patients with SSRD. Patients presenting between September 2016 and September 2018 were included in the study.

Patients were excluded if they were <18 years old, had an IQ < 80, had a diagnosis of a substance use disorder, or objected to the use of their anonymised treatment data for research purposes. The intake procedure has been described extensively elsewhere [Van der Feltz-Cornelis, 2020] and is summarised here. At intake, participants underwent physical examination including a neurological component. To confirm that the DSM-5 criteria for SSRD was met, participants underwent semi structured psychiatric evaluation and psycho-diagnostic assessment with the Mini-International-Neuropsychiatric-Interview [Sheehan DV et al., 1998] and final DSM-5 classification to be laid down in the medical file was decided based on those in a multidisciplinary team meeting. This classification of SSRD was used for the study. Severity of anxiety, depression, pain and physical symptoms were assessed using the generalised Anxiety-Disorder-7 (GAD7), Patient-Health-Questionnaire-9 (PHQ-9), Brief-Pain-Inventory (BPI) and Physical-Symptom-Questionnaire-51 (PSQ-51) (see Table 1), respectively [Spitzer RL et al., 2006; Kroenke JB et al., 2001; Tan G et al., 2004; Van Hemert, A.M. 2003]. In case of no clinical signs of active infection at intake, serum hsCRP and IL-6 were taken by venepuncture to confirm this or otherwise to address clinically.

Venepuncture was performed at 12:00pm, according to a immunological lab protocol to measure hsCRP and IL-6 at intake. Specimens were drawn from participants and frozen at 80 C until thawed for assay. Plasma levels of IL-6 were measured by high sensitivity enzyme linked immunosorbent assay (ELISA; Quantikine HS ELISA R&D systems HS600B) performed by DS2, Dynex Elisa robot automated analyzers. Intra assay precision CV% was in the interval 6.9–7.8; interassay precision CV% was in the interval 6.5–9.6. The detection range of this assay was 0.02–10 pg/ml. For hsCRP, immunoturbidimetry by automated analyzers was performed. The declared detection limit was 0.20 mg/l [Van Der Feltz-Cornelis et al., 2020].

Data were analysed of the participants who continued to receive treatment after intake. This treatment regimen has been described extensively elsewhere [de Vroege, L et al., 2019] and is summarised here. Treatment consisted of cognitive behavioural therapy (CBT) in combination with pharmacotherapy for comorbid depression, anxiety disorder or pain, in combination with physical therapy. This type of treatment is suggested by the multidisciplinary guideline for medically unexplained symptoms and somatic symptom Disorder [van der Feltz-Cornelis CM et al., 2012; van der Feltz-Cornelis CM et al., 2011] and in two Cochrane Reviews [Kleinstäuber M et al., 2014; van Dessel N et al., 2014] and was provided following a Shared Decision Making model. During treatment, every 6 weeks symptoms were monitored and discussed with patients in order to assess if the treatment was still on target or needed to be adapted [van der Feltz-Cornelis CM et al., 2014]. Participants were followed up at end of treatment. In order to decrease patient burden, to allow for shared decision making, and to take heterogeneity of conditions within SSRD into account, patients were given the option to repeat at least two of GAD7, PHQ-9, BPI and PSQ-51 questionnaires, depending on which symptoms they felt affected them most. On average, treatment lasted 12 months.

2.1. Statistical analysis

Data analysis was performed in the Statistical-Package-for-the-Social-Sciences (SPSS) version 26 [IBM Corp 2020]. Descriptive statistics were used to summarise the sample and baseline scores.

Linear regression models were used to investigate the relationship

Table 1
Outcome measures and moderators.

Symptom Questionnaire	Description
GAD7	GAD7 is a 7 question 4-point- questionnaire that measures anxiety symptoms over the last 2 weeks. Scores can range from 0 to 21. A score of 5–9 is suggestive of mild anxiety, 10–14 moderate anxiety and ≥15 severe anxiety [Spitzer, R.L et al., 2006].
PHQ-9	PHQ-9 is a 9 question 4-point questionnaire that measures depressive symptoms over the last 2 weeks. Scores can range from 0 to 27. A score of 5–9 is suggestive of mild depression, 10–14 moderate depression, 15–19 moderate to severe depression and ≥20 severe depression [Kroenke, K et al., 2001].
BPI	Brief pain inventory (BPI) is a 9 question interval scale questionnaire that measures pain symptoms over the last 24 h. Scores can range from 0 to 10. A scores of 1–4 suggest mild pain, 5–6 moderate pain and 7–10 severe pain [Tan, G et al., 2004].
PSQ-51	The PSQ-51 is designed to assess the number and severity of 51 somatic symptoms across a variety of systems. 1 point is scored for every symptom the participant reports [Van Hemert, A.M. 2003]. The PSQ-51 has similar diagnostic value to the hospital anxiety and depression score, proving to be highly sensitive in identifying somatoform and anxiety/depressive disorders in the primary care setting.PSQ-51 is a 51-point questionnaire that measures the frequency and severity of physical symptoms present over the last week. Scores range from 0 to 51. It consists of 13 gastrointestinal, 11 neurological, 14 autonomic and 8 musculoskeletal questions, each assessed on a 0–3 4 point Likert scale for the presence and severity of symptoms. Symptoms are only scored if they are ranked as either 2 or 3 on the Likert scale, hence the total score is out of 51, scoring 1 for each symptom reported. Higher scores are suggestive of more frequent and severe physical symptoms. Previous research has identified that a PSQ-51 score of 5 or more is considered high and proved a useful indicator of somatoform disorder and/or anxiety/depressive disorder [de Waal, M.W.M. et al., 2009].
Psychiatric and physical examination	Participants underwent complete physical examination including a neurological component. To confirm that the DSM-5 criteria for SSRD were met, participants underwent semi structured psychiatric evaluation and psycho-diagnostic assessment with the MINI-international-neuropsychiatric-interview [Sheehan, D.V et al., 1998] and final DSM-5 classification to be laid down in the medical file was decided based on those in a multidisciplinary team meeting. This classification of SSRD was used for the study [Sheehan, D.V et al., 1998].
hsCRP and IL-6	In case of no clinical signs of active infection at intake, serum hsCRP and IL-6 were taken by venepuncture to confirm this or otherwise to address clinically. Specimens were stored at −80 °C. Serum IL-6 was measured using high sensitivity enzyme linked immunosorbent assay (ELISA); Quantikine HS ELISA R&D systems HS600B), this was completed by DS2, Dynex Elisa robot automated analyzers. Intra assay precision CV% was 6.9–7.8; interassay precision CV% was 6.5–9.6. The detection range was 0.02–10 pg/ml. With regards to hsCRP, automated analyzers were used to perform immunoturbidimetry. Detection limit was 0.2 mg/l [Van Der Feltz-Cornelis, CM et al., 2020].

PHQ = patient health questionnaire-9; GAD7 – generalised anxiety disorder assessment-7; BPI = brief pain index; PSQ-51 = physical symptom

questionnaire-51; MINI = Mini International Neuropsychiatric Interview; SSRD = somatic syndrome and related disorders.

between follow-up questionnaire score and baseline IL-6 and hsCRP. The models were adjusted for age, gender, whether or not they had a somatic comorbidity, and baseline questionnaire score [Clifton and Clifton, 2019]. The dependent variables were PHQ-9 score, GAD7 score, BPI score and PSQ-51 at follow up. The analyses were conducted separately for IL-6 and hsCRP. . A significance level of 5% was used for all the analyses.

Model checking was performed graphically, using scatter plot, q-q plot and histograms to ensure all models met assumptions of linearity, absence of outliers, independence of observations, homoscedasticity and normal distribution of residuals. Adjusted R-squared values were calculated to ensure models were a good fit for the data.

3. Results

3.1. Summary statistics

Table 2 shows the summary statistics for overall data and data used in analysis. The total sample consisted of 237 patients with an average age of 42 years, ranging from 18 to 80 years.

The cohort was 59.5% female and the most common diagnosis was SSD (73.8%), followed by SSD with predominant pain (14.3%). The least common diagnostic categories were illness anxiety (5.9%) and CD/FND (5.9%). 55.9% of patients had somatic comorbidity such as arthritis, rheumatological or cardio-pulmonary disease. Our cohort showed varying degrees of inflammation and both hsCRP and IL-6 showed a positive skew. Mean baseline hsCRP was 3.70 mg/l (SD 4.55) Mean baseline IL-6 was 2.52 pg/l (SD 3.85). One outlier was excluded for an IL-6 value of 226.00 pg/l.

At end of treatment 200 participants reported PHQ-9, 128 GAD7, 226 BPI and 135 PSQ-51. On average there was an improvement from baseline to follow up across all measures. The mean change in PHQ-9 score was −2.18 (95% CI -2.90, −1.44); GAD7 score was −3.27 (95% CI -4.18, −2.37); BPI score was −0.54 (95% CI -0.89, −0.17) mean change in PSQ-51 score was −2.99 (95% CI -4.28, −1.70) (Table 3). All changes were significant. As can be seen in Table 2, the average GAD7 score dropped from above to below 10, which is a clinically relevant change from disorder level to non-disorder level anxiety symptoms [Spitzer RL et al., 2006].

3.2. Analysis

As shown in Table 3, there was evidence to support an association between baseline hsCRP and follow-up PSQ-51 score (p = 0.030). The model predicted that for every 1 mg/l increase in baseline hsCRP, PSQ-51 score was higher by 0.301 point at follow-up. The analyses found no evidence to suggest any significant relationship between serum hsCRP and GAD7, PHQ-9 or BPI score follow up scores.

There was no evidence to support a relationship between baseline IL-6 score and any of the follow-up questionnaire scores at end of treatment. Adjustment for age, gender and somatic comorbidity showed no significant change in the association.

4. Discussion

4.1. Summary of findings

These were exploratory analyses, but we did find significant evidence to support an association between higher baseline hsCRP scores and higher scores in the PSQ-51 questionnaire at end of treatment. In our data, for every 1 mg/l higher in baseline hsCRP, the number of physical symptoms were higher by 0.301 at follow-up.

We did not find any statistically significant relationship between baseline IL-6 and symptom outcome at end of treatment.

4.2. Interpretation of the results

From a clinical perspective, understanding disease prognosis has useful implications to patient management, particularly with identifying high-risk patients who may require a more multidisciplinary approach towards their care. Our findings suggest that high baseline serum hsCRP but not IL-6 might be associated with a greater burden of physical symptoms, but not depression, anxiety or pain symptoms at end of treatment in SSRD. The strength of the association is 0.301 in terms of risk for sustained high somatic symptoms. This is highly relevant as the presence of somatic symptoms and associated emotions, cognitions and behaviour expressing distress are required for a diagnosis of SSRD, but not necessarily anxiety or depression per se [American Psychiatric Association 2013].

Given this, there may be two explanations to our findings:

Since hsCRP has been associated with active symptom burden in SSRD, greater baseline hsCRP could reflect individuals with more aggressive inflammation, potentially resulting in sustained somatic symptom burden [Van Der Feltz-Cornelis, CM et al., 2020].

Table 2
Demographic and summary statistics for study population. Summary statistics for change scores.

Overall summary statistics at baseline								
	N	Mean	SD	Minimum	Maximum	Percentiles		
						25	**50**	**75**
Age	237	42.57	13.27	18	80	32	41	51
hsCRP	229	3.70	4.55	0.20	31.14	0.83	2.20	4.63
IL-6	202	2.52	3.85	0.62	48.00	1.17	1.76	2.73
Baseline PHQ-9	224	14.26	6.14	0	27	9	14	19
Baseline GAD7	227	11.65	5.37	0	21	7	11	16
Baseline BPI	226	5.65	2.52	0	10	4	6	8
Baseline PSQ-51	227	16.43	8.93	0	45	10	15	23

	N	Baseline Mean (SD)	Follow-up Mean (SD)	Change Mean (95% CI)
PHQ-9	200	14.25 (6.04)	12.08 (7.06)	−2.16 (−2.90, −1.44)
GAD7	128	11.42 (5.07)	8.15 (6.06)	−3.27 (−4.18, −2.37)
BPI	135	5.74 (2.44)	5.21 (2.51)	−0.53 (−.89, −.17)
PSQ-51	135	14.43 (8.20)	11.44 (9.69)	−2.99 (−4.28, −1.70)

N = number; SD = standard deviation; 95% CI = 95% confidence interval; SSRD = somatic syndrome and related disorders; SSD = somatic syndrome disorder; hsCRP = high sensitivity C-reactive protein; IL-6 = interleukin-6; PHQ = patient health questionnaire-9; GAD7 – generalised anxiety disorder assessment-7; BPI = brief pain index; PSQ-51 = physical symptom questionnaire-51.

Table 3
Adjusted linear regression models of follow-up questionnaire scores against baseline serum hsCRP and baseline IL-6.

Coefficients							
Model		Unstandardized coefficients		p value	95% CI for B		Adjusted R square
		B	Std. Error		Lower bound	Upper bound	
Baseline serum hsCRP							
Follow-up PSQ-51 score (N = 95)	(Constant)	−4.109	2.579	.115	−9.235	1.016	0.567
	hsCRP	0.301	.136	.030	.030	.571	
	Age	0.030	.053	.570	−.075	.136	
	Female	0.802	1.501	.595	−2.181	3.785	
	Somatic comorbidity	−0.452	1.422	.752	−3.278	2.375	
	Baseline PSQ-51	.893	.086	.000	.722	1.064	
Follow-up GAD7 score (N = 123)	(Constant)	1.825	1.867	.330	−1.872	5.522	0.313
	hsCRP	.065	.097	.502	−.127	.257	
	Age	−.036	.036	.326	−.107	.036	
	Female	−1.291	.958	.181	−3.188	.607	
	Somatic comorbidity	.504	.936	.591	−1.350	2.359	
	Baseline_GAD7	.679	.091	.000	.499	.859	
Follow-up PHQ-9 score (N = 192)	(Constant)	.203	1.659	.903	−3.071	3.477	0.447
	hsCRP	−.046	.082	.572	−.208	.115	
	Age	−.002	.029	.941	−.060	.055	
	Female	.725	.778	.353	−.811	2.260	
	Somatic comorbidity	.872	.778	.264	−.663	2.406	
	Baseline PHQ-9	.798	.064	.000	.672	.924	
Follow-up BPI score (N = 133)	(Constant)	1.518	.692	.030	.148	2.888	0.374
	hsCRP	.023	.035	.516	−.047	.092	
	Age	.002	.014	.893	−.026	.030	
	Female	−.285	.363	.434	−1.004	.434	
	Somatic comorbidity	−.024	.361	.947	−.738	.690	
	Baseline BPI	.624	.074	.000	.477	.771	
Baseline serum IL-6							
Follow-up PSQ-51 score (N = 75)	(Constant)	−4.328	3.028	.157	−10.369	1.712	.527
	IL-6	−.115	.138	.410	−.391	.161	
	Age	.050	.063	.432	−.076	.176	
	Female	2.043	1.827	.267	−1.601	5.687	
	Somatic comorbidity	.447	1.665	.789	−2.875	3.769	
	Baseline PSQ-51	.917	.103	.000	.711	1.123	
Follow-up GAD7 score (N = 104)	(Constant)	1.624	2.008	.421	−2.360	5.608	.316
	IL-6	−.047	.101	.640	−.247	.152	
	Age	−.038	.039	.338	−.116	.040	
	Female	−.865	1.044	.410	−2.938	1.208	
	Somatic comorbidity	1.183	1.012	.245	−.825	3.192	
	Baseline_GAD7	.693	.100	.000	.493	.892	
Follow-up PHQ-9 score (N = 169)	(Constant)	−.718	1.688	.671	−4.051	2.615	.510
	IL-6	−.109	.092	.238	−0.291	0.073	
	Age	.003	.030	.922	−0.056	0.062	
	Female	1.063	.786	.178	−0.490	2.615	
	Somatic comorbidity	1.207	.784	.126	−0.342	2.756	
	Baseline PHQ-9	.817	.062	.000	0.694	0.940	
Follow-up BPI score (N = 111)	(Constant)	1.534	.811	.061	−.073	3.142	.340
	IL-6	−.061	.040	.125	−.139	.017	
	Age	.004	.016	.801	−.027	.035	
	Female	−.186	.406	.647	−.990	.618	
	Somatic comorbidity	.228	.400	.570	−.566	1.022	
	Baseline BPI	.617	.085	.000	.449	.785	

Age, gender and baseline questionnaire score as covariates. *$p < 0.05$.
PHQ = patient health questionnaire-9; GAD7 – generalised anxiety disorder assessment-7; BPI = brief pain index; PSQ-51 = physical symptom questionnaire-51; B = beta; 95% CI = 95% confidence interval; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6.

Secondly, SLI may only play a role in some conditions within SSRD, and not others. If so, compared to those without SLI, patients with SLI may have a worse prognosis, due to a current lack of treatment options addressing SLI in SSRD.

In any case, it seems that hsCRP might act as a valid marker of future somatic symptom burden in SSRD patients, even in the presence of somatic comorbidity.

4.3. Future research

In terms of identifying potential avenues for further research, an interesting observation is that IL-6 did not seem to be associated with symptom prognosis in any domain. Although CRP production is primarily IL-6 dependent, Tumour-Necrosis-Factor-α (TNF-α) and interleukin 1β (IL-1β) also play a role [Tanaka, T et al., 2014]. Given that earlier research by our group identified that elevated TNF-α but not IL-1β was associated with CD/FND [Van Der Feltz-Cornelis, CM et al., 2021], the role of TNF-α might play an important role the pathogenesis of SSRD. This warrants further investigation, including exploring the role of TNF-α inhibitors in SSRD with SLI. Interestingly, patients with SLI and depression have shown promising response to ketamine, TNF-α inhibitor and minocycline treatment [Walker AJ et al., 2015; Raison CL et al., 2013; Uzzan and Azab, 2021; Nettis, M.A et al., 2021]. These may also be useful candidates to explore in the treatment of patients with SSRD and SLI.

Also, genomic and serological studies addressing the roles of hsCRP and related biomarkers such as TNF-a in SSRD pathogenesis might be conducted. This might help identify candidate molecules for a more personalised approach towards treatment, in addition to building a more complete neuroinflammatory model of SSRD pathogenesis. We recommend that for studies investigating the roles of anti-inflammatory agents in SSRD, moderator analysis for inflammation should be conducted. This may help us understand why individuals with elevated hsCRP show less improvement in physical symptoms after treatment.

Furthermore, replication is required on a larger scale to evaluate whether SLI is applicable to SSRD in general, or if it is specific to conditions within SSRD.

hsCRP might also be useful in conjunction with other factors in stratifying risk and functional outcome in SSRD patients. The REGARDS study has already highlighted the prognostic value of hsCRP in predicting cardiovascular disease and stroke. Alone, hsCRP was not clinically useful in stratifying cardiovascular risk, probably due to its non-specific and heterogenous nature [Howard, V. J et al., 2005]. However, when combined with other factors in the Framingham risk score, addition of hsCRP led to improvement in risk stratification for cardiovascular disease [Ridker, P. M., & Cook, N. 2004]. Based on results for the JUPITER study, the role of hsCRP in targeted statin therapy and clinical decision making in stroke and heart disease remains controversial and up for debate [Ridker, P.M. et al., 2008]. With these lessons in mind, and given that the variance of the association is moderate [Cohen and Seconded, 1988], it is important to recognise that hsCRP likely plays a partial role in risk stratification for SSRD, or might be relevant in certain groups and that other factors should be used in conjunction with hsCRP during risk stratification and clinical decision making. This makes a case for further research exploring the possible role of hsCRP in conjunction with other factors, as clinical biomarker for personalisation of treatment in SSRD and other conditions. In addition, it highlights the importance of identifying personalised treatment options for SLI in SSRD.

4.4. Strengths and limitations

There are a number of strengths to the study design. Patients were screened for any evidence of infection at intake, thus allowing for identifying patients with as yet unknown active inflammatory conditions. The size of the cohort and the prospective design also allowed for exploration of hsCRP and IL-6 as prognostic markers in SSRD for the first time. Furthermore, we were able to control for somatic comorbidity.

However, there are also limitations. Elevated hsCRP has been associated with smoking, obesity and various environmental factors. [Tiina M. et al., 2008]. We were unable to control for these factors.

The majority of our participants had a diagnosis of SSD, with only small number with diagnoses of illness anxiety and CD/FND. Also, our sample included patients with and without somatic comorbidity and found this to be of no influence to the association. This may have contributed to the heterogeneity in hsCRP and IL-6 in our sample.

Finally, given the sample originates from a center of excellence for SSRD, and that is a last resort for such patients in the Netherlands, the findings in this study are not generalizable to the entire SSRD population, but rather to complex patients with a long-term diagnosis of SSD [van Eck van der Sluijs JF et al., 2017].

5. Conclusion

Our analysis identified that baseline serum hsCRP may be associated with a greater burden of physical symptoms in SSRD patients, after approximately one year of treatment. There was no evidence that baseline hsCRP was associated with the burden of depression, anxiety or pain at one year follow up. There also appeared to be no relationship between baseline serum IL-6 and depression, anxiety, physical or pain symptoms at one year follow up. These findings warrant further research on how a combination of baseline serum hsCRP and other demographic factors might play a role in early identification of SSRD patients who are at risk of persistently high physical symptom burden. Furthermore, these findings support further exploration of a neuroinflammatory model of SSRD pathogenesis, highlighting the possibility of targeted anti-inflammatory therapies as a potential treatment avenue in patients with SLI.

Author contributions

William Heseltine-Carp MBBCh, conceptualization, methodology, formal analysis, Writing - Original Draft, Writing - Review & Editing.

Veronica Dale MSc, methodology, formal analysis, Writing - Review & Editing.

Jonna van Eck van der Sluijs, MD, PhD, validation, investigation, data curation, supervision, Writing - Review & Editing.

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Statement of ethics

According to Dutch law, in accordance with the World Medical Association's Helsinki Declaration, and according to the Dutch Central Medical Ethical Committee, no explicit informed consent is required for the use of clinical or administrative data, collected in the context of treatment provision. For the present research we used data that were collected for administrative purposes and monitoring of treatment outcome by treatment providers. At intake at CLGG, patients were informed that Patient Reported Outcome Measures (PROM) and medical data obtained during intake and treatment could be used for research evaluation on an anonymous basis, unless they indicated their dissent. In case of dissent, this was notified in the patient file. Patient files of dissenting patients were excluded from the study. Data were coded in order to create an anonymous dataset. The research protocol was approved by the scientific committee of GGz Breburg (2019–01).

Data availability statement

The data are owned by a third party, GGz Breburg, that does not

publicly share data. However, interested parties will be able to obtain data upon request as follows. Researchers can submit a research plan, which describes the background and methods of a proposed research question, and a request for specific data of the database used for this study to answer the research question. After approval of the research plan by the principal investigator and the director of GGz Breburg, a de-identified minimal dataset can be obtained. Information can be requested by contacting the principal investigator.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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Fig. 1 was made with MindtheGraph, www.mindthegraph.com.

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