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Wirsching Psychosocial Risk Scale (WPRS) *Versus* Outcome in Patients With Breast Disease and Breast Cancer: A Prospective 25-year Follow-up Study in Patients With Breast Cancer Symptoms

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Abstract

Background/Aim: This study evaluated whether Wirsching Psychosocial Risk (WPR) scale for measuring the severity of psychosocial risk (PR) factors can predict the long-term outcomes in patients having breast carcinoma (BC) symptoms.

Patients and Methods: A total of 115 patients with BC symptoms completed the WPR scale and associations between WPR scale and long-term outcome were analyzed using survival models.

Results: The WPRS scores correlated to Beck Depression Inventory (BDI) *(r*=0.382, *p*<0.001), to Montgomery-Asberg Depression Rating Scale (MADRS) *(r*=0.517, *p*<0.001), to Forsen inventory (FI) during 0-2 years *(r*=0.392, *p*<0.001) and FI 2-6 years *(r*=0.397, *p*<0.001) prodromal periods and to State-Trait Anxiety inventory (STAI) *(r*=0.131, *p*=0.164*)* levels. In the Cox model, the WPR scale predicted the 25-year relapse-free survival (RFS) in patients with BC [hazard ratio (HR)=1.76, *p*=0.197] and the WPR scale predicted 25-year overall survival (OS) in women with BC symptoms (HR=2.31, *p*=0.019) and women with BC (HR=2.12, *p*=0.09). In the Kaplan-Meier survival analysis by the log-rank test, the 25-year relapse rate differed between low WPRS score (<21) *versus* the high WPRS score (≥21) in patients with BC (37.5% *versus* 20%, log-rank *p*-value=0.195). Also, the low WPRS score (<21) was a favorable predictor of RFS [HR=1.50, 95% confidence interval (CI)=0.80-2.99, *p*=0.199] in the patients with BC symptoms. The 25-year OS rate differed significantly between low WPRS score (<21) *versus* high WPRS score (≥21) patients with BC symptoms (74.4% *versus* 53.0%, log-rank *p*-value=0.016). A similar pattern was seen in patients with BC as the WPRS score predicted 25-year OS in women with BC (45.8% *versus* 20.0%, log-rank *p*-value=0.088).

continued

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Conclusion: The studies assessing the impact of PR factors on outcome of patients with BC symptoms have not reported WPRS levels. In the present study, a 25-year follow-up of patients with BC symptoms enables us to detect the 25-year outcome and to assess the RFS and OS *versus* WPRS approach using Kaplan-Meier and Cox proportional hazard models. The study showed that the PR variables detected with the WPR scale significantly correlate to the 25-year OS in patients with BC and 25-year OS in patients with BC symptoms. Therefore, the use of WPRS inventory detecting PR factors should be considered as a useful part of the diagnostic protocol of patients with BC symptoms.

Keywords: Psychosocial risk, Wirsching scale, breast cancer symptoms, long-term outcome.

Introduction

Breast carcinoma (BC) is the most common carcinoma in women (1-5) and one of the main public health problems worldwide (6, 7). Although several risk factors for BC (8-10) have been identified, the role of life stressors remains unclear on etiology and outcome of BC (11-13). Beliefs about the causes of BC in general appear to vary widely and are often inaccurate (14). For example, fewer than half of the respondents in one national survey by Breslow *et al*. (15) were able to correctly identify a single risk factor for a variety of cancers. Similarly, fewer than half of the female cancer survivors in a study by Wold *et al.* (16) believed that physical inactivity, obesity, and diet were important causes of BC. Findings from the National Cancer Institute's Health Information National Trends Survey further demonstrate that beliefs about the causal role of lifestyle behaviors vary across cancer sites and therefore individuals are often unaware or may not believe in cancer causes or risk factors that are modifiable through behavior change. In a study by Wang *et al.* (17), heredity (84.4%) was ranked as the most important causal factor, followed by the changes in one's immune system (60.6%), smoking (58.3%), pollution in the environment (57.6%), aging (48.8%), diet or eating habits (46.4%), lack of exercise (35.7%), alcohol (29.9%), stress (27.5%) and prior breast surgery (23.7%).

At present, there is few evidence for any biological assumption (18-20) through which psychosocial risk (PR) factors could predict the etiology or outcome in patients having BC. However, several possible mechanisms have been suggested, most of these hypotheses implicate hormonal status or immunological functions (21-25).

The findings from the above-mentioned studies motivated us to conduct the current study with the aim of searching an association between the features of PR detected with the WPR scale *versus* the 25-year relapse-free survival (RFS) and the overall survival (OS) in women diagnosed in Breast Cancer Diagnostic Unit (BCDU) of Kuopio University hospital. No previous studies are available, where the outcome of the PR factors with the WPRS approach had been estimated using survival models.

Patients and Methods

Patients. The study cohort included 115 patients with BC symptoms diagnosed in BCDU, KUH, Finland, of whom 34 (29.6%) were patients with BC and 81 non-BC patients (70.4%) (Table I). The detailed description of the study protocol is shown in earlier reports by Ollonen *et al.* (26-29). The Kuopio Breast Cancer (KBC) study is a multidisciplinary cooperative project conducted by different departments of the UEF and KUH. The participants of the project included all women who were referred to KUH for breast examination between April 1990 and December 1995. The KBC study follows the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by the European Institute of Oncology in Milan and was initiated as a SEARCH program of the International Agency for Research on Cancer. The collaborative study is based on the assumption that BC and colorectal cancer may have common risk factors.

Wirsching Psychosocial Risk Scale (WPRS). We used a modified WPRS for psychosocial risk assessment (30-

Table I. *The baseline data and mean score values of different quality of life scales in three study groups; HSP, BC, BBD.*

Variable	HSP (n=28)	BBD (n=53)	BC (n=34)	*p*-Value
Age (mean, years)	45.7	47.6	51.6	0.12
Height (mean, cm)	160.8	162.3	164.4	0.75
Body weight (mean, kg)	68.3	67.8	72.5	0.25
Age at menarche (mean, years)	13.4	13.4	13.4	0.99
Age at birth of I child (mean, years)	25.0	25.0	25.2	0.92
Age at menopause (mean, years)	50.0	48.9	47.9	0.53
No. of children (mean)	2.5	2.4	2.6	0.27
Parous	23 (82%)	44 (83%)	31 (91%)	0.50
Breast feeding (mean, months)	3.9	3.4	3.6	0.77
Use of oral contraceptives	18 (64%)	25 (47%)	13 (38%)	0.12
HRT	14 (50%)	36 (68%)	27 (79%)	0.44
Premenopausal	18 (64%)	28 (53%)	13 (38%)	0.10
Postmenopausal	10 (36%)	25 (47%)	21 (62%)	0.12
History of previous BBD	10 (36%)	22 (42%)	18 (53%)	0.37
Family history of BC	5 (18%)	5 (9%)	1 (3%)	0.21
Use of alcohol	13 (46%)	31 (58%)	21 (62%)	0.44
Smoking	10 (36%)	21 (40%)	15 (44%)	0.80
BDI (mean score)	7.8	8.5	8.9	0.70
MADRS (mean score)	22.2	21.2	21.2	0.78
STAI (mean score)	39.2	41.3	40.1	0.29
FI, 0-2 years (mean score)	14.3	14.2	14.1	0.99
FI, 2-6 years (mean score)	12.5	11.8	9.8	0.43
SAI	27.2	28.7	24.0	0.003
WPRS	17.2	17.6	19.4	0.05

HSP: Healthy study participants; BC: breast carcinoma; BBD: benign breast disease; HRT: hormonal replacement therapy; FI: Forsen inventory; SAI: Sifneos alexithymia inventory; WPRS: Wirsching psychosocial risk scale.

32) with 10 scales; each scale has subscales from grade 1 to grade 5. The researchers estimated the patients' psychosocial risk, and the test was rated as follows: grade I (subscale grade 3), low psychosocial risk; grade II (subscale grade 2 and subscale grade 4), moderate psychosocial risk; grade III (subscale grade 1 and subscale grade 5), high psychosocial risk for BC. All patients completed the WPRS with ten variables listed in Table II and each variable classified into five grades. A detailed description of the WPRS protocol is shown in earlier reports (30-32).

Sifneos Alexithymia Inventory (SAI) for alexithymic characteristics. A detailed description of the SAI scale is shown in earlier reports (33, 34).

Forsen (FI) psychological stress (PS) inventory. A detailed description of the FI scale is shown in earlier reports (35-37).

Beck Depression Inventory (BDI). A detailed description of the BDI score protocol is shown in earlier reports (38-40).

Montgomery-Asberg Depression Rating Scale (MADRS). A detailed description of the MADRS score protocol is shown in earlier reports (41-43).

Spielberger State-Trait Anxiety inventory (STAI). A detailed description of the STAI score protocol is shown in earlier reports (44, 45).

Statistical analysis. Baseline group differences were analyzed by two-sided chi-square and non-parametric Kruskall-Wallis tests. RFS was calculated from the time of diagnosis to the occurrence of the first relapse, contralateral BC, or metastatic disease. OS was assessed as the time from the date of diagnosis to the date of last follow-up or death of the

Table II. *The ten variables according to WPRS.*

A. Psychosocial stress (m227)	F. Rationalizing attitude (m221)
1. Severe stress (n=23)	1. Highly rationalizing (n=14)
2. Apathy (n=10)	2. Rationalizing (n=50)
3. Moderate stress (n=39)	3. Balanced (n=32)
4. Weak stress (n=7)	4. Emotional (n=19)
5. No stress (n=36)	5. Highly balanced (n=0)
B. Suppression of feelings (m225)	G. Harmonizing behavior (m223)
1. Negative (n=18)	1. Harmonic (n=19)
2. Repressive (n=56)	2. Controlled (n=51)
3. Adequate (n=36)	3. Adequate (n=43)
4. Outbursting (n=3)	4. Aggressive (n=1)
5. Labile (n=2)	5. Hostile (n=1)
C. Optimism (m218)	H. Altruism (m224)
1. Hopeless (n=12)	1. Devoted (n=18)
2. Pessimistic (n=44)	2. Careful (n=45)
3. Realistic (n=35)	3. Normal (n=48)
4. Optimistic (n=18)	4. Demanding (n=4)
5. Euphoric (n=6)	5. Egoistic (n=0)
D. Self-sufficiency (m219)	I. Anxiety (m222)
1. Helpless (n=25)	1. Panic (n=0)
2. Dependent (n=51)	2. Anxious (n=38)
3. Balanced (n=30)	3. Troubled (n=56)
4. Independent (n=9)	4. Trouble-free (n=19)
5. Self-supporting (n=0)	5. Brave (n=2)
E. Remoteness (m220)	J. Cares about her health (m226)
1. Longing to be alone (n=13)	1. Ruining her health (n=2)
2. Reserved (n=38)	2. Unconcerned about her health (n=33)
3. Communicating (n=41)	3. Fair (n=73)
4. Social (n=9)	4. Cares about her health (n=5)
5. Talkative (n=14)	5. Hypochondric (n=2)

WPRS: Wirsching psychosocial risk scale.

patient. The effect of the WPRS protocol on the RFS and OS were calculated using the Kaplan-Meier survival analysis and the difference between the groups was assessed using the log-rank test. The *p*-values and the hazard ratios (HRs) with their 95% confidence intervals (CI) were calculated using the Cox proportional hazard models. Pearson's method was used to test for correlation between WPRS scores and SAI, FI, STAI, BDI and MADRS scale values. Data were analyzed using the IBM SPSS statistical software (IBM SPSS Statistics for Windows, version 26.0, IBM Corporation Armonk, NY, USA).

Results

BDI, MADRS, STAI, FI, SAI and WPRS levels in BC and non-BC patients. The baseline data and mean score values of BDI, MADRS, STAI, FI and SAI scales in three study groups; HSP, BBD and BC are presented in Table I. The mean BDI, MADRS, STAI, FI scale (0-2 years) and FI scale (2-6 years) values between BC and non-BC patients were quite similar (p=0.70, 0.78, 0.29, 0.99, 0.43, respectively, Table I). The mean SAI score values were significantly higher in non-BC patients (HSP=27.2 and BBD=28.7) *versus* BC patients (24.0, p=0.003, Table I). The mean WPRS levels were significantly higher in BC patients (19.4, p=0.05, Table I) *versus* non-BC patients (HSP=17.2 and BBD=17.6). The WPRS levels correlated to BDI (r=0.382, p<0.001), to MADRS (r=0.517, p<0.001, Figure 1), to FI during 0-2 years *(r*=0.392, p<0.001) and FI 2-6 years (r=0.397, p<0.001) prodromal periods and to STAI (r=0.131*, p*=0.164*)* levels.

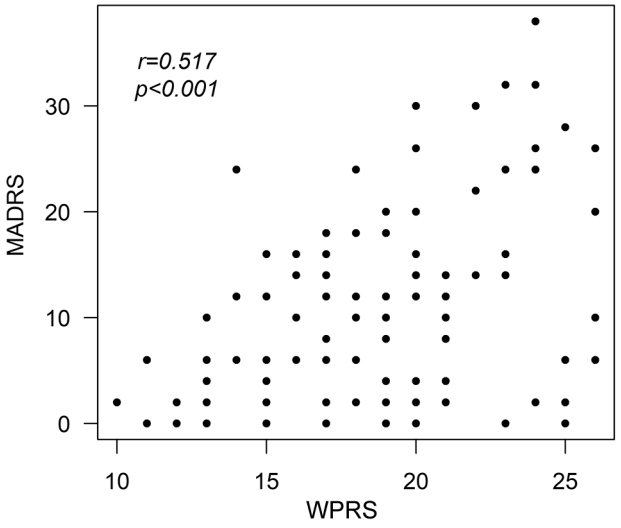

Figure 1. *Scatter plot of Wirsching's psychosocial risk scale (WPRS) score levels versus Montgomery-Asberg depression rating scale (MADRS) score levels in patients with breast cancer symptoms (r=0.517, p<0.001).*

The 25-year RFS and OS. In the Cox model, the WPRS inventory predicted the 25-year RFS in patients with BC (HR=1.76, p=0.197) and the WPRS predicted 25-year OS in women with BC symptoms (HR=2.31, p=0.019) and women with BC (HR=2.12, p=0.09). In the Kaplan-Meier survival analysis by the log-rank test, the 25-year relapse rate differed between low WPRS levels (<21) *versus* the high WPRS levels (≥21) in patients with BC (37.5%

Table III. *Relapse-free survival (RFS) according to Wirsching psychosocial risk scale (WPRS) scores in total participants (All) and in HSP (n=28), BBD (n=53), and BC (n=34) groups.*

Group	RFS (%)		HR	95% CI	*p*-Value
	WPRS ≤21	WPRS >21			
All	63.3	52.0	1.50	0.80-2.99	0.199
HSP	70.8	60.0	1.67	0.34-8.26	0.533
BBD	73.8	80.0	0.79	0.18-3.57	0.759
BC	37.5	20.0	1.76	0.75-4.17	0.197

p-Values and hazard ratios (HRs) and their 95% confidence intervals (CI) were calculated from the Cox proportional hazard models.

Table IV. *Overall survival (OS) according to Wirsching psychosocial risk scale (WPRS) scores in total participants (All) and in HSP (n=28), BBD (n=53), and BC (n=34) groups.*

Group	OS (%)		HR	95% CI	*p*-Value
	WPRS ≤21	WPRS >21			
All	74.4	53.0	2.31	1.15-4.65	0.019 (Figure 2)
HSP	87.5	60.0	3.63	0.61-21.7	0.158
BBD	83.3	80.0	1.32	0.28-6.38	0.727
BC	45.8	20.0	2.12	0.87-5.16	0.09 (Figure 3)

p-Values and hazard ratios (HRs) and their 95% confidence intervals (CI) were calculated from the Cox proportional hazard models.

versus 20%, log-rank *p*-value=0.195; Table III). Also, the low WPRS levels (<21) showed as a favorable predictor of the RFS (HR=1.50, 95% CI=0.80-2.99, *p*=0.199; Table IV) in the patients with BC symptoms. The 25-year OS rate differed significantly between low WPRS levels (<21) *versus* the high WPRS levels (≥21) patients with BC symptoms (74.4% *versus* 53.0%, log-rank *p*-value=0.016, Figure 2). A similar pattern was seen in patients with BC as the WPRS predicted 25-year OS in women with BC (45.8% *versus* 20.0%, log-rank *p*-value=0.088, Figure 3).

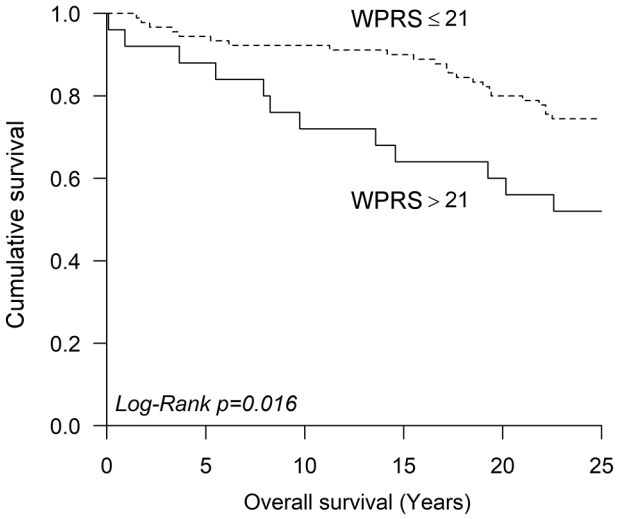

Figure 2. *The Kaplan-Meier survival curves for overall survival (OS) in all patients with breast cancer symptoms (n=115) according to Wirsching's psychosocial risk scale (WPRS). The WPRS score was a continuous variable in the analysis of study patients. The WPRS score had a significant effect on OS by the log-rank test (p=0.016).*

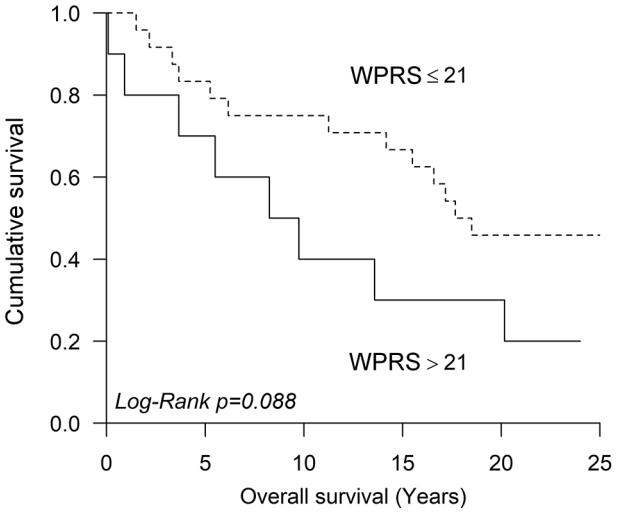

Figure 3. *The Kaplan-Meier survival curves for overall survival (OS) in patients with breast cancer (n=34) according to Wirsching's psychosocial risk scale (WPRS). The WPRS score was a continuous variable in the analysis of study patients. The WPRS score had almost statistically significant effect on OS by the log-rank test (p=0.088).*

Discussion

At present, there is few evidence for any biological assumption through which PR factors could predict the etiology or outcome in patients having BC. Several possible mechanisms have been suggested, most of these hypotheses implicate hormonal status or immunological functions of patients (18-26).

Raison *et al.* (18) reviewed studies reporting increased levels of inflammatory biomarkers in patients with major depressive disorder (MDD) *versus* nondepressed individuals. According to the review, they suggest that MDD may partly be an inflammatory condition.

Hashmi *et al.* (19) studied brain activity in patients with back pain in 2 months prodromal period *versus* patients with no back pain in 12 months prodromal period. Their results showed that there is association between back pain and brain activity (BA), since the location of BA shifted from regions involved in acute pain to chronic pain locations. Authors provided a time window (6-12 months) for the stabilization of this signature, which could be a specific 'functional biomarker' for long-term back pain. Thus, their results have important clinical implications regarding the optimal time window for treatments targeting its prevention.

Duric *et al.* (21) reviewed the recent evidence of stress *versus* activation of the immune response system and release of common proinflammatory mediators. They suggest that there is need for research to find any biological mechanism through which PR factors could predict the outcome in disease.

Miller *et al.* (22) investigated whether depression is associated with cellular immunity in patients with MDD (n=32 patients) *versus* 32 healthy female control participants. In addition, they tried to identify neuroendocrine and behavioral pathways that might account for this relationship. The study groups were matched for age and none of the participants were taking medication, and all participants were free of disease involving the immune system. The patients with MDD had reduced proliferative responses to the mitogens concanavalin A and phytohemagglutinin compared with control participants. Depression was also associated with greater tobacco and caffeine consumption, less physical activity, and poorer sleep quality.

Gerdin *et al.* (23) studied the effects of acute PS factors on human colorectal mucosal barrier function and stress-induced modulation of mucosal immunity. Healthy volunteers were submitted to acute PS and colorectal mucosal biopsies were obtained to assess the impact of PS factors on barrier function. Authors found that PS factors increased paracellular permeability in the colorectal mucosa of healthy study participants. Authors concluded that there is a link between PS factors and increased intestinal permeability in human colorectal mucosa and stress and barrier dysfunction are contributing factors in gastrointestinal diseases.

La Torre *et al.* (24) reviewed the mechanisms that are involved in stress-induced intestinal permeability changes. An impaired intestinal barrier function can be harmful, because it allows the translocation of luminal antigens and toxins into the subepithelial tissue and bloodstream, which may lead to local and systemic immune responses. The reviewed *in vitro* and *in vivo* studies suggest that the PS factors can increase intestinal permeability via mast-cell dependent mechanisms and interfere with intestinal barrier integrity. However, authors admit that the results are difficult to compare, because animal and human studies vary highly in both PS type and duration and intestinal permeability measure.

Hilakivi-Clarke *et al.* (14, 24) investigated the association between social isolation (ISO) and BC and suggested ISO as risk factor for BC. Authors defined ISO as loneliness or an absence of perceived social connections (14, 24). The same authors (25) recently reported that ISO factors could activate inflammatory and mitochondrial metabolic pathways in the Sague Dawley rat mammary gland leading to BC. The authors concluded that the immune system appears to play an important role as a mediator between personality and cancer (13, 24, 25). In line with this hypothesis, recent randomized controlled trial suggests that women with increased IL-8 levels have decreased depressive symptoms in BC (46). Moreover, levels of C-reactive protein (CRP) were inversely correlated with the cognitive efficiency cluster in BC (47). However, polymorphisms in genes regulating neuroplasticity may change inflammation-associated cognitive depressive symptoms in BC (48). Interestingly, increased emotional distress and stress even in daughters of BC patients was associated with decreased natural cytotoxic activity, elevated levels of stress hormones and decreased secretion of Th1 cytokines (49).

The findings from the above-mentioned studies motivated us to conduct the current study with the aim of searching an association between PS events detected with WPRS scoring *versus* the 25-year outcome with RFS and OS in women with BC symptoms diagnosed in BCDU. No previous studies are available where the outcome of the PS events with the WPRS approach had been estimated using survival models.

Taken together, the aim was to investigate the characteristics of the PR events with the WPRS model in women with BC symptoms and to report their link with outcome. The results showed that the PR events detected with WPRS scale correlate to the 25-year OS in the women with BC and women with BC symptoms. The present data indicate that the WPRS protocol seem to have the potential to enhance the DA of the PR testing in women with BC symptoms.

Conclusion

Various risk factors for BC have been identified, many of which are related to reproductive characteristics, hormonal physiology, and life-style. The studies to date assessing PR events on outcome of women with BC have not considered WPRS inventory. Until now, the lack of long follow-up time of women with BC has delayed the advance in survival model calculations. The follow-up of women with BC symptoms enables us to detect the 25-year outcome and to assess the RFS and OS *versus* PR events detected with WPRS approach using survival models. The present study showed that the PR events detected with the WPRS significantly correlate to the 25-year OS in patients with BC and in patients with BC symptoms. Therefore, the use of WPRS protocol detecting PR events should be considered as a useful part of the diagnostic protocol of patients with BC symptoms.

Conflicts of Interest

The Authors report no conflicts of interest or financial ties regarding this study.

Authors' Contributions

All Authors contributed to the collection and analysis of data, drafting and revising the manuscript, and read and approved the final article.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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