Evaluation and predictive factors analyses for patient-self-reported depression, anxiety and quality of life in patients with metastatic renal cell carcinoma underwent interferon-α treatment: a prospective cohort study

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Background: This study aimed to investigate the patient-self-reported depression, anxiety and quality of life (QoL) as well as their predictive factors in patients with metastatic renal cell carcinoma (mRCC) underwent interferon-alpha (IFN-α) treatment.

Methods: A total of 127 patients with mRCC underwent IFN-α treatment were consecutively enrolled in this prospective cohort study. Anxiety, depression and QoL were assessed at week 0 (W0), W4, W8 and W12 by Hospital Anxiety and Depression Scale (HADS) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 Scale), respectively.

Results: The percentages of anxiety and depression both increased at W12 compared with W0. The EORTC QLQ-C30 Scale-Global health status score, EORTC QLQ-C30 Scale-Function and EORTC QLQ-C30 Scale-Symptoms scores did not deteriorate at W4, W8 or W12 compared with W0. Multivariate logistic regression analyses revealed that older age and elevated level of highest education independently predict reduced risk of HADS-Anxiety score elevation at W12, while hypertension was an independent predictive factor for increased risk. Older age also independently associated with less risk of elevated HADS-Depression score. Smoke, hypertension, diabetes and higher ECOG performance were independent predicting factors for escalated risk of EORTC QLQ-C30 Scale-Global health status score elevation at W12, and higher ECOG performance was an independent predicting factor for increased risk of elevated EORTC QLQ-C30 Scale-Function score at W12.

Conclusions: In conclusion, anxiety and depression increased while QoL did not deteriorate in mRCC patients during IFN-α treatment, and age, highest education, hypertension, smoke, diabetes as well as higher ECOG performance status correlated with their aggravation.

Keywords: Metastatic renal cell carcinoma (mRCC); interferon-alpha; anxiety; depression; quality of life; predictive factor

Introduction

Renal cell carcinoma (RCC), the ninth most frequent carcinoma in males all over the world according to the report of Global Cancer Statistics in 2012, presents with an escalating incidence in the past decade worldwide especially in more developed countries (1-3). In China, there were estimated 668,000 new RCC cases in 2015 consisting of 432,000 male patients and 236,000 female patients, and 234,000 RCC related deaths including 152,000 male cases as well as 82,000 female cases (4). Among all RCC cases, metastatic RCC (mRCC) accounts for approximately 30% of all RCC cases, for which the treatment goal is to relieve symptoms and prolong survival (5). Although the treatment options for mRCC has altered from comprehensive immunosuppressive therapy to targeted therapy and new immunosuppressive drugs, due to good treatment responses observed by clinical studies, interferon-alpha (IFN-α) is still the most commonly applied drug in mRCC patients (6,7).

However, the problems concerning psychiatric status and quality of life (QoL) in mRCC patients treated by IFN-α are drawing increasing attention among oncologists due to that a growing number of mood disorders and change of QoL have been reported (8,9). Unstable psychiatric status in mRCC patients mainly refers to anxiety and depression, which could be evaluated by numerous scales such as Hospital Anxiety and Depression Scale (HADS), a self-assessed scale generally applicable in cancer patients (10,11). As another crucial aspect, QoL is already extensively assessed in patients with other malignancies for the purpose of evaluating and improving symptoms, physical function and life satisfaction after various treatments including IFN-α therapy (12-14). Unfortunately, insufficient clue for reducing the risk of depression, anxiety and decrease of QoL in mRCC patient through identifying the predicting factors is accessible for clinicians until now.

Thus, the aim of our study was to investigate the patient-self-reported depression, anxiety and QoL as well as their predictive factors in patients with mRCC underwent IFN-α treatment.

Methods

Participants

A total of 127 patients with mRCC underwent IFN-α treatment at the Department of Urinary Surgery in Harbin Medical University Cancer Hospital between Jan 2013 and Dec 2016 were consecutively enrolled in this prospective cohort study. Inclusion criteria were as follows: (I) diagnosed as mRCC according to clinical, imaging and pathological findings; (II) age above 18 years; (III) about to receive IFN-α treatment; (IV) life expectancy longer than 12 months; (V) able to be followed up regularly and complete the assessment questionnaires. Patients were excluded if they (I) had brain metastasis; (II) accompanied with other solid tumors or hematological malignance; (III) had uncontrolled hypertension, severe infection or primary organ failure; (IV) were pregnant or lactating, or planned for pregnancy.

Ethics

This study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital and conducted according to the Helsinki Declaration. The number of the Ethic Approval was KY2012-12. All patients provided written informed consents.

Baseline data collection

After the enrollment, patients' baseline characteristics were collected, which included age, gender, highest education, body mass index (BMI), overweight, smoke, drink, hypertension, hyperlipidemia, diabetes, Eastern Cooperative Oncology Group (ECOG) performance, histology, number of metastatic sites, location of metastatic sites, tumor size, prior radiotherapy and prior chemotherapy.

Treatment

This prospective cohort study did not intervene treatments of patients. All patients underwent IFN-α treatment "on demand" according to disease conditions and patients willingness. The common treatment was as follows: 9MU IFN-α by subcutaneous injection 3 times/week for 12 weeks.

Assessments of anxiety and depression

The anxiety and depression of patients were assessed at week 0 (W0), W4, W8 and W12 by Hospital Anxiety and Depression Scale (HADS) anxiety (HADS-Anxiety) score and depression (HADS-Depression) score. Both HADS-Anxiety and HADS-Depression consist of seven questions which were scored as 0–3 points individually, resulting in 0–21 points and being classified as: 0–7, no anxiety/depression; 8–10, light anxiety/depression; 11–14, moderate
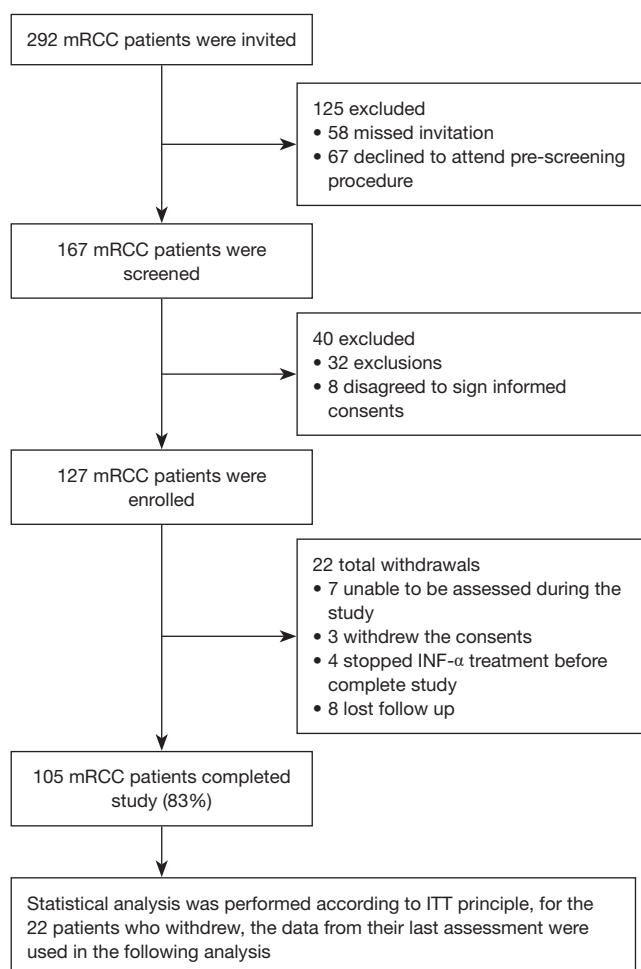
1462

Wang et al. Predictive factors for anxiety, depression and QoL in mRCC patients

Figure 1 Study flow. MRCC, metastatic renal cell carcinoma.

anxiety/depression; 15–21, severe anxiety/depression (15).

Assessments of quality of life

We used European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 Scale) to assess the QoL of patients at W0, W4, W8 and W12. The EORTC QLQ-C30 Scale is a 30-item instrument with a four-point scale, from "not at all" to "very much", for items 1 to 28; and a seven-point scale for items 29 and 30. The QLQ-C30 could be divided into 15 domains including 5 functioning domains (physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning), 3 symptoms domains (fatigue, pain, nausea and vomiting), 1 global health status/quality of life and 6 single items (each item as a domain). All raw data were transformed to

a 0 to 100 point scale. Higher scores in the global health status scale and functional scale indicated better health state and functioning, while higher score in the symptom scale indicated excessive symptoms (16).

Definitions

According to the assessment criteria of the HADS-Anxiety score, HADS-Depression score and EORTC QLQ-C30 Scale, the elevation of HADS-Anxiety score, HADS-Depression score and EORTC QLQ-C30 Scale-Symptoms score indicate aggravating anxiety, depression and symptoms, respectively. And the reduction of EORTC QLQ-C30 Scale-Global health status score as well as EORTC QLQ-C30 Scale-Functions score suggest loss of quality of life and functions, respectively. In order to evaluate the predictive factors of pejorative indexes, including HADS-Anxiety score, HADS-Depression score and EORTC QLQ-C30 Scale scores at W12, we defined the following changes of the indexes mentioned above as events: (I) the elevation of HADS-Anxiety score, HADS-Depression score and EORTC QLQ-C30 Scale-Symptoms score at W12 compared to W0; (II) the reduction of EORTC QLQ-C30 Scale-Global health status score and EORTC QLQ-C30 Scale-Functions score at W12 compared to W0.

Statistics

Statistical analysis was performed using SPSS 22.0 software (IBM, Corp., Ltd, USA) and GraphPad Prism 6.0 software (GraphPad Software Inc., USA). All analyses were performed based on the intention-to-treat (ITT) principles with the last observation carried forward (LOCF) method from any of the three post-baseline measures. As for the 22 patients who withdrew, the data from their last assessment were used in the following analysis. Comparison between each visit was determined by paired t-test or McNemar test. Univariate and multivariate logistic regression analyses were performed to evaluate the factors affecting the aggravation of HADS score and EORTC QLQ-C30 Scale score. $P<0.05$ was considered significant.

Results

Study flow

As shown in *Figure 1*, 292 mRCC patients were initially

Table 1 Baseline characteristics of patients with mRCC

Items	mRCC patients (N=127)
Age (years)	54.87±11.15
Gender (male/female)	101/26
Highest education	
Primary school or less	68 (53.5)
High school	40 (31.5)
Undergraduate or above	19 (15.0)
BMI (kg/m^2)	24.71±2.61
Overweight (BMI >24 kg/m^2)	75 (59.1)
Smoke	49 (38.6)
Drink	43 (33.9)
Hypertension	87 (68.5)
Hyperlipidemia	66 (52.0)
Diabetes	18 (14.2)
ECOG performance	
0	96 (75.6)
1	29 (22.8)
2	2 (1.6)
Histology	
Clear RCC	103 (81.1)
Others	24 (18.9)
Number of metastatic site	
1	120 (94.5)
>1	7 (5.5)
Location of metastatic site	
Lung	84 (66.0)
Liver	11 (8.7)
Bone	11 (8.7)
Others	14 (11.0)
Lung and liver	3 (2.4)
Lung and bone	2 (1.6)
Lung and others	1 (0.8)
Liver and bone	1 (0.8)
Tumor size >7 cm	56 (44.1)
Prior radiotherapy	4 (3.1)
Prior chemotherapy	1 (0.8)
HADS-Anxiety score	5.80±3.17
No anxiety (HADS-Anxiety score 0–7)	99 (78.0)
Anxiety (HADS-Anxiety score 8–21)	28 (22.0)
HADS-Anxiety grade	
Light (HADS-Anxiety score 8–10)	18 (14.1)
Moderate (HADS-Anxiety score 11–14)	8 (6.3)

Table 1 (*continued*)

Table 1 (*continued*)

Items	mRCC patients (N=127)
Severe (HADS-Anxiety score 15–21)	2 (1.6)
HADS-Depression score	6.43±3.81
No depression (HADS-Depression score 0–7)	87 (68.5)
Depression (HADS-Depression score 8–21)	40 (31.5)
HADS-Depression grade	
Light (HADS-Depression score 8–10)	23 (18.1)
Moderate (HADS-Depression score 11–14)	11 (8.7)
Severe (HADS-Depression score 15–21)	6 (4.7)
EORTC QLQ-C30 Scale	
Global health status score	63.98±14.25
Functions score	69.42±18.59
Symptoms score	29.83±15.45

Data was presented as mean value ± standard deviation or count (percentage). mRCC, metastatic renal cell carcinoma; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30 Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

invited and 125 patients were excluded due to that there were 58 patients missed invitation and 67 patients declined to attend pre-screening procedure. Afterwards, 167 mRCC patients were screened for eligibility and 40 patients were excluded (32 exclusions and 8 disagreed to sign informed consents), so the remaining 127 mRCC patients were enrolled in our study. Among the 127 mRCC patients, there were 22 withdrawals including 7 patients unable to be assessed during the study, 3 patients withdrew the consents, 4 patients stopped IFN-α treatment before complete study and 8 patients lost to follow up, thus leaving 105 mRCC patients completed the whole study which accounted for 83% of our cohort. As for the 22 withdrew patients, the data collected from their last assessments were used in the following analysis. The statistical analysis was performed according to the ITT principles using the LOCF method.

Baseline characteristics

The mean age of the total 127 mRCC patients was 54.87±11.15 years, among whom there were 101 males and 26 females (*Table 1*). And the numbers of patients had the

1464

Wang et al. Predictive factors for anxiety, depression and QoL in mRCC patients
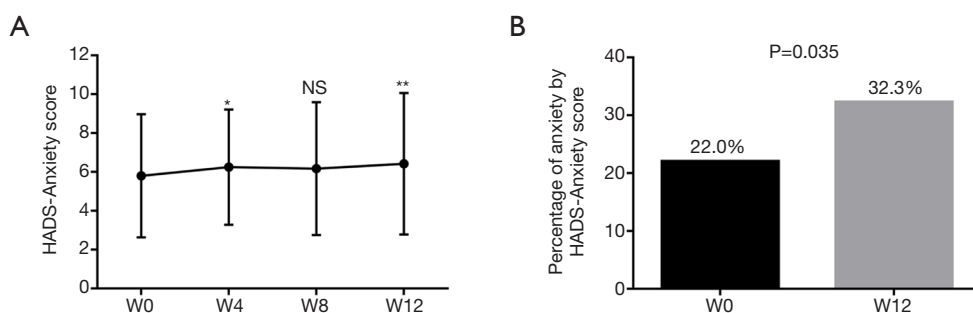

Figure 2 Change of HADS-Anxiety score. HADS-Anxiety score was higher at W4 and W12 compared with W0, while no difference was observed between W8 and W0 (A), and the percentage of patients had anxiety evaluated by HADS-Anxiety score was increased at W12 compared with W0 (B). Comparison between two groups was determined by paired *t* test. P<0.05 was considered significant. HADS, Hospital Anxiety and Depression Scale. *P<0.05; **P<0.01; NS, not significant.
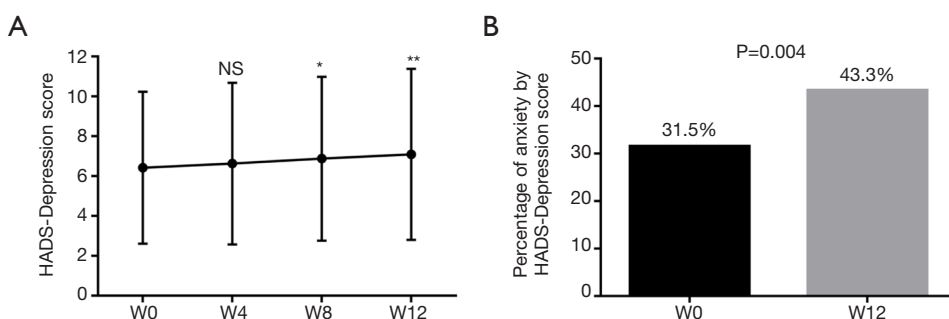

Figure 3 Change of HADS-Depression score. HADS-Depression score increased at W8 and W12, however, it was of no difference at W4 compared with W0 (A), and the percentage of patients had depression assessed by HADS-Depression score was elevated at W12 compared with W0 (B). Comparison between two groups was determined by paired t test. P<0.05 was considered significant. HADS, Hospital Anxiety and Depression Scale. *P<0.05; **P<0.01; NS, not significant.

highest education of primary school or less, high school and undergraduate or above were 68 (53.5%), 40 (31.5%) and 19 (15.0%), respectively. The mean value of BMI and the number of overweight patients were 24.71±2.61 kg/m^2 and 75 (59.1%), respectively. And the number of patients had ECOG performance score of 0, 1 and 2 were 96 (75.6%), 29 (22.8%) and 2 (1.6%), respectively. In addition, there were 103 (81.1%) patients had clear RCC and 24 (18.9%) patients had other RCCs. And the numbers of patients had 1 and >1 metastatic site were 120 (94.5%) and 7 (5.5%), respectively. The other information of medical history, clinicopathological features, HADS and EORTC QLQ-C30 Scale scores at baseline were listed in *Table 1*.

Change of HADS-Anxiety score and HADS-depression score

As presented in *Figure 2*, the HADS-Anxiety score increased

at W4 (P<0.05) and W12 (P<0.01) compared with W0, while no difference was observed between W8 and W0 (P>0.05) (*Figure 2A*). At W12, the percentage of patients had anxiety assessed by HADS-Anxiety score was elevated compared with W0 (32.3% *vs.* 22.0%, P=0.035) (*Figure 2B*). The HADS-Depression score was higher at W8 (P<0.05) and W12 (P<0.01) than that of W0, however, the HADS-Depression score at W4 was of no difference compared with W0 (*Figure 3A*). And the proportion of patients had depression assessed by HADS-Depression score was increased at W12 than that of W0 (43.3% *vs.* 31.5%, P=0.004) (*Figure 3B*).

Change of EORTC QLQ-C30 Scale scores

The EORTC QLQ-C30 Scale-Global health status score did not change at W4, W8 or W12 compared to W0 (all
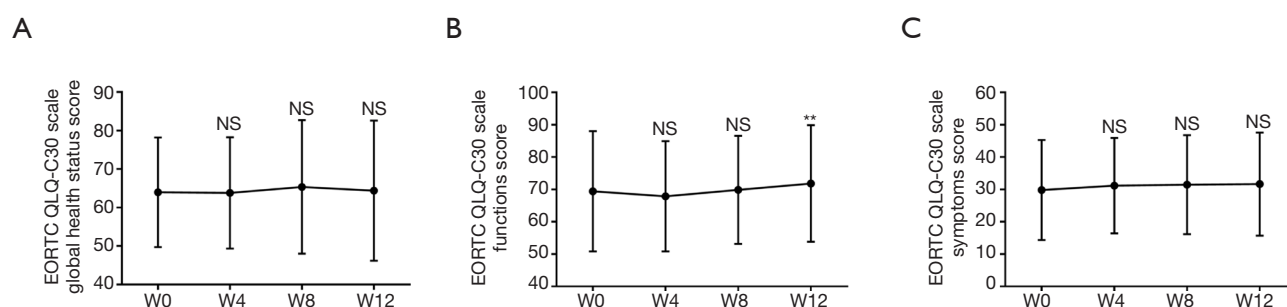
Figure 4 Change of EORTC QLQ-C30 Scale scores. The EORTC QLQ-C30 Scale-Global health status score (A) and EORTC QLQ-C30 Scale-Symptoms scores (C) did not vary at W4, W8 or W12 compared to W0. The EORTC QLQ-C30 Scale-Function score increased at W12 while was similar to W0 at W4 and W8 (B). Comparison between two groups was determined by paired t test. $P<0.05$ was considered significant. EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. **$P<0.01$; NS, not significant.

Table 2 Number of patients with changed HADS-Anxiety, HADS-Depression and EORTC QLQ-C30 Scale scores from week 0 (W0) to week 12 (W12)

Scores	Patients
HADS-Anxiety score	
Elevated	64 (50.4)
Reduced	36 (28.3)
Unchanged	27 (21.3)
HADS-Depression score	
Elevated	62 (48.8)
Reduced	34 (26.8)
Unchanged	31 (24.4)
EORTC QLQ-C30 Scale-Global health status score	
Elevated	52 (40.9)
Reduced	51 (40.2)
Unchanged	24 (18.9)
EORTC QLQ-C30 Scale-Functions score	
Elevated	67 (52.8)
Reduced	52 (40.9)
Unchanged	8 (6.3)
EORTC QLQ-C30 Scale-Symptoms score	
Elevated	67 (52.8)
Reduced	57 (44.9)
Unchanged	3 (2.3)

Data was presented as count (percentage). HADS, Hospital Anxiety and Depression Scale; EORTC QLQ-C30 Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

$P>0.05$) (*Figure 4A*). As to EORTC QLQ-C30 Scale-Function score, it increased at W12 ($P<0.01$) compared to W0, while was similar to W0 at W4 ($P>0.05$) and W8 ($P>0.05$) (*Figure 4B*). As shown in *Figure 4C*, the EORTC QLQ-C30 Scale-Symptoms scores at W4 ($P>0.05$), W8 ($P>0.05$) and W12 ($P>0.05$) were similar to that of W0.

Change of HADS scores and EORTC QLQ-C30 Scale scores from W12 to W0

The numbers of patients had elevated, reduced and unchanged HADS scores and EORTC QLQ-C30 scores at W12 compared with W0 were displayed in *Table 2*. Sixty-four (50.4%), 36 (28.3%) and 27 (21.3%) patients had elevated, reduced and unchanged HADS-Anxiety score, and the numbers of patients with elevated, reduced and unchanged HADS-Depression score were 62 (48.8%), 34 (26.8%) and 31 (24.4%), respectively. In addition, the numbers of patients had elevated, reduced and unchanged EORTC QLQ-C30 Scale-Global health status score were 52 (40.9%), 51 (40.2%) and 24 (18.9%), respectively. As for ORTC QLQ-C30 Scale-Function score, it was elevated in 67 (52.8%) patients, reduced in 52 (40.9%) patients and unchanged in 8 (6.3%) patients. And the figures of patients with elevated, reduced and unchanged ORTC QLQ-C30 Scale-Symptoms score were 67 (52.8%), 57 (44.9%) and 3 (2.3%), respectively.

Factors affecting the aggravation of HADS scores at W12

In order to observe the predictive factors for the aggravation of HADS scores, univariate and multivariate logistic regression analyses were conducted. As displayed in *Table 3*,

1466

Wang et al. Predictive factors for anxiety, depression and QoL in mRCC patients

Table 3 Factors affecting the elevation of HADS-Anxiety score at week 12 (W12) compared to week 0 (W0) by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age	0.006	0.952	0.919–0.986	<0.001	0.878	0.822–0.938
Gender (male)	0.029	0.428	0.200–0.918	0.356	0.637	0.244–1.659
Higher highest education	0.298	0.775	0.480–1.252	0.005	0.314	0.140–0.705
BMI	0.073	1.136	0.988–1.305	0.716	1.055	0.791–1.406
Overweight	0.010	2.605	1.256–5.403	0.343	2.019	0.473–8.612
Smoke	0.401	1.360	0.664–2.786	0.686	1.202	0.493–2.931
Drink	0.901	1.048	0.502–2.185	0.707	1.198	0.467–3.071
Hypertension	0.007	2.942	1.339–6.465	0.009	3.903	1.414–10.774
Hyperlipidemia	0.331	1.414	0.703–2.845	0.915	0.953	0.389–2.333
Diabetes	0.637	1.273	0.467–3.470	0.396	1.760	0.477–6.488
Higher ECOG performance	0.376	1.401	0.664–2.953	0.402	1.541	0.560–4.237
Histology (clear RCC vs. others)	0.344	1.543	0.628–3.791	0.364	1.705	0.539–5.392
Number of metastatic site (>1 vs. 1)	0.714	1.333	0.286–6.214	0.325	2.524	0.400–15.947
Metastatic site (lung vs. others)	0.521	1.286	0.597–2.770	0.632	1.285	0.461–3.581
Tumor size >7 cm	0.781	1.105	0.548–2.227	0.959	1.024	0.412–2.547
Prior radiotherapy	0.340	3.049	0.309–30.129	0.082	18.059	0.689–473.357
Prior chemotherapy	1.000	–	0.000	1.000	–	0.000

Data was presented as P value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting the elevation of HADS-Anxiety score at week 12 (W12) compared to week 0 (W0) were determined by univariate and multivariate logistic regression model analysis. Highest education was scored as: primary school or less =0, high school =1 and undergraduate or above =2. P value <0.05 was considered significant. HADS, Hospital Anxiety and Depression Scale; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

univariate logistic regression analysis revealed that older age (P=0.006) and gender male (P=0.029) correlated with less risk of elevated HADS-Anxiety score at W12, while overweight (P=0.010) and hypertension (P=0.007) associated with higher risk of increased HADS-Anxiety score at W12. All factors were included in the multivariate logistic regression analysis, which disclosed that older age (P<0.001) and elevated level of highest education (P=0.005) independently predict reduced risk of HADS-Anxiety score elevation at W12, while hypertension (P=0.009) was an independent predictive factor for increased risk.

As for the predicting factors for elevated HADS-Depression score, univariate logistic regression analysis disclosed that age (P=0.014), gender male (P=0.005) and metastatic site at lung (P=0.022) associated with limited risk of elevated HADS-Depression score (*Table 4*). All factors were included in the multivariate logistic regression

analysis, which showed that age (P=0.005) independently associated with less risk of elevated HADS-Depression score.

Factors affecting the aggravation of EORTC QLQ-C30 Scale scores at W12

In order to assess the predictive factors for the aggravation of EORTC QLQ-C30 Scale scores (the reductions of EORTC QLQ-C30 Scale-Global health status score and EORTC QLQ-C30 Scale-Functions score, and the elevation of EORTC QLQ-C30 Scale-Symptoms score), univariate and multivariate logistic regression analyses were performed. As exhibited in *Table 5*, gender male (P=0.050) and metastatic site at lung (P=0.043) correlated with decreased risk of EORTC QLQ-C30 Scale-Global health status score reduction at W12, however, smoke (P=0.020),

Table 4 Factors affecting the elevation of HADS-Depression score at week 12 (W12) compared to week 0 (W0) by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age	0.014	0.958	0.926–0.991	0.005	0.933	0.889–0.980
Gender (male)	0.005	0.333	0.154–0.723	0.085	0.451	0.182–1.117
Higher highest education	0.615	0.885	0.549–1.425	0.073	0.542	0.278–1.058
BMI	0.296	0.930	0.812–1.065	0.099	0.786	0.590–1.046
Overweight	0.889	1.052	0.518–2.134	0.095	3.439	0.806–14.681
Smoke	0.449	1.319	0.644–2.699	0.918	0.956	0.407–2.244
Drink	0.705	1.152	0.552–2.404	0.838	0.911	0.374–2.218
Hypertension	0.335	1.450	0.681–3.084	0.383	1.490	0.608–3.649
Hyperlipidemia	0.938	0.973	0.485–1.951	0.792	1.124	0.470–2.688
Diabetes	0.914	1.057	0.390–2.865	0.655	0.748	0.209–2.672
Higher ECOG performance	0.281	1.508	0.714–3.185	0.733	1.171	0.473–2.897
Histology (clear RCC *vs.* others)	0.561	0.768	0.315–1.872	0.129	0.437	0.150–1.274
Number of metastatic site (>1 *vs.* 1)	0.235	2.763	0.516–14.804	0.069	5.919	0.873–40.144
Metastatic site (lung *vs.* others)	0.022	0.396	0.179–0.876	0.149	0.493	0.188–1.287
Tumor size >7 cm	0.813	1.088	0.540–2.193	0.717	1.169	0.501–2.727
Prior radiotherapy	0.354	0.339	0.034–3.348	0.192	0.184	0.015–2.337
Prior chemotherapy	1.000	–	0.000	1.000	–	0.000

Data was presented as P value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting the elevation of HADS-Depression score at week 12 (W12) compared to week 0 (W0) were determined by univariate and multivariate logistic regression model analysis. Highest education was scored as: primary school or less =0, high school =1 and undergraduate or above =2. P value <0.05 was considered significant. HADS, Hospital Anxiety and Depression Scale; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

hypertension (P=0.007), diabetes (P=0.018) and higher ECOG performance status (P=0.005) correlated with higher risk. And multivariate logistic regression analysis revealed that smoke (P=0.037), hypertension (P=0.003), diabetes (P=0.011) and higher ECOG performance status (P=0.004) were independent predicting factors for escalated risk of EORTC QLQ-C30 Scale-Global health status score reduction at W12.

As for the predictive factors for risk of the reduced EORTC QLQ-C30 Scale-Function score at W12, univariate logistic regression analysis showed that higher ECOG performance status (P=0.016) correlated with increased risk of reduced EORTC QLQ-C30 Scale-Function score at W12 (*Table 6*). Subsequently, all factors with a P value <0.1 were analyzed by the multivariate

logistic regression analysis, which disclosed that higher ECOG performance status (P=0.026) was an independent predicting factor for increased risk of reduction of EORTC QLQ-C30 Scale-Function score at W12.

As to the EORTC QLQ-C30 Scale-Symptoms score, univariate and multivariate logistic regression analyses were performed to assess the predictive factors for its aggravation as well. As presented in *Table 7*, the univariate logistic regression analysis displayed that overweight (P=0.021) correlated with increased risk of EORTC QLQ-C30 Scale-Symptoms score increment at W12. All factors were included in the multivariate logistic regression analysis, while no factor was revealed as an independent predictive factor for elevated EORTC QLQ-C30 Scale-Symptoms score at W12.

Table 5 Factors affecting the reduction of EORTC QLQ-C30 Scale-Global health status score at week 12 (W12) compared to week 0 (W0) by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age	0.538	1.010	0.978–1.043	0.500	1.018	0.967–1.070
Gender (male)	0.050	0.471	0.222–1.000	0.341	0.623	0.235–1.651
Higher highest education	0.566	0.866	0.531–1.414	0.593	1.221	0.587–2.539
BMI	0.824	0.985	0.859–1.129	0.892	0.980	0.734–1.309
Overweight	0.489	1.293	0.625–2.673	0.539	1.617	0.350–7.476
Smoke	0.020	2.397	1.149–5.000	0.037	2.613	1.061–6.439
Drink	0.508	1.286	0.610–2.712	0.098	2.307	0.858–6.204
Hypertension	0.007	3.215	1.370–7.544	0.003	5.078	1.737–14.843
Hyperlipidemia	0.857	1.067	0.525–2.172	0.272	0.588	0.228–1.517
Diabetes	0.018	3.590	1.249–10.313	0.011	6.794	1.557–29.651
Higher ECOG performance	0.005	3.170	1.430–7.028	0.004	4.715	1.665–13.357
Histology (clear RCC *vs.* others)	0.768	1.148	0.460–2.865	0.479	1.549	0.461–5.203
Number of metastatic site (>1 *vs.* 1)	0.355	2.071	0.443–9.671	0.106	4.483	0.727–27.638
Metastatic site (lung *vs.* others)	0.043	0.447	0.205–0.973	0.078	0.388	0.136–1.113
Tumor size >7 cm	0.202	1.595	0.779–3.264	0.354	1.560	0.609–3.995
Prior radiotherapy	0.538	0.487	0.049–4.813	0.595	2.052	0.145–29.056
Prior chemotherapy	1.000	–	0.000	1.000	–	0.000

Data was presented as P value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting the reduction of EORTC QLQ-C30 Scale-Global health status score at week 12 (W12) compared to week 0 (W0) were determined by univariate and multivariate logistic regression model analysis. Highest education was scored as: primary school or less =0, high school =1 and undergraduate or above =2. P value <0.05 was considered significant. EORTC QLQ-C30 Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

Discussion

In our study, we found that: (I) in mRCC patients treated by IFN-α, the HADS-Anxiety score was elevated at W4 and W12, HADS-Depression score was higher at W8 and W12 compared with W0, and the anxiety and depression percentages were both increased at W12 than that of W0. In addition, the EORTC QLQ-Global health status score, EORTC QLQ-Symptoms score and ORTC QLQ-Function score did not vary at W4, W8 or W12 compared with W0; (II) multivariate logistic regression disclosed that older age and elevated level of highest education were independent predictive factors for reduced risk of HADS-Anxiety score elevation, while hypertension was independently associated with increased risk. Additionally, older age was an independent predictive factor for decreased

risk of HADS-Depression score elevation; (III) as for EORTC QLQ scores, the multivariate logistic regression illuminated that smoke, hypertension, diabetes and higher ECOG performance independently predicted increased risk of reduced EORTC QLQ-Global health score, and higher ECOG performance was also an independent predictive factor for EORTC QLQ-Function score reduction, while no factor independently correlated with the aggravation of EORTC QLQ-C30 Scale-Symptoms score at W12.

As a grievous condition and a major threat to human, cancer directly or indirectly causes mood disorders to patients as a consequence of a large reduction of life expectancy, side effect of anti-tumor drugs and a change of quality of life (11,17,18). For instance, in a recent cohort study in Indonesia, the researchers discover an obvious decline in anxiety level and an increase of QoL

Table 6 Factors affecting the reduction of EORTC QLQ-C30 Scale-Functions score at week 12 (W12) compared to week 0 (W0) by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age	0.364	0.985	0.954–1.017	0.528	0.986	0.945–1.029
Gender (male)	0.758	0.889	0.420–1.881	0.675	1.208	0.498–2.930
Higher highest education	0.451	1.203	0.744–1.947	0.676	1.142	0.613–2.130
BMI	0.759	0.979	0.854–1.122	0.913	0.986	0.759–1.279
Overweight	0.915	1.040	0.506–2.136	0.964	0.969	0.252–3.728
Smoke	0.257	0.653	0.312–1.366	0.073	0.457	0.194–1.074
Drink	0.321	0.681	0.318–1.456	0.439	0.714	0.303–1.679
Hypertension	0.593	1.233	0.572–2.659	0.726	1.166	0.493–2.760
Hyperlipidemia	0.476	1.295	0.637–2.634	0.654	1.211	0.524–2.798
Diabetes	0.179	1.994	0.729–5.456	0.101	2.681	0.824–8.728
Higher ECOG performance	0.016	2.587	1.190–5.624	0.026	2.731	1.126–6.624
Histology (clear RCC *vs.* others)	0.703	1.194	0.479–2.981	0.873	0.918	0.325–2.598
Number of metastatic site (>1 *vs.* 1)	0.916	1.087	0.233–5.072	0.984	1.018	0.175–5.927
Metastatic site (lung *vs.* others)	0.736	0.875	0.403–1.900	0.942	1.035	0.414–2.589
Tumor size >7 cm	0.067	1.958	0.955–4.017	0.137	1.867	0.820–4.249
Prior radiotherapy	0.710	1.460	0.199–10.710	0.675	1.611	0.173–14.997
Prior chemotherapy	1.000	0.000	0.000	1.000	0.000	0.000

Data was presented as P value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting the reduction of EORTC QLQ-C30 Scale-Functions score at week 12 (W12) compared to week 0 (W0) were determined by univariate and multivariate logistic regression model analysis. Highest education was scored as: primary school or less =0, high school =1 and undergraduate or above =2. P value <0.05 was considered significant. EORTC QLQ-C30 Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

in oral squamous cell carcinoma patients treated by chemotherapy or invasive therapies (19). Despite that meta-analysis demonstrate encouraging treatment responses and reduced mortality rate in mRCC patients treated by IFN-α compared with placebo or non-immunosuppressive therapies, anxiety and depression are still frequently observed in clinical practice and clinical studies (20,21). Nonetheless, studies investigating the incidences of anxiety and depression of mRCC patients treated by IFN-α are rare, most of those studies are conducted on patients with hepatitis. In a prospective cohort study enrolls patients with hepatitis C treated by pegylated interferon (PEG-IFN)-based treatment, they find that there are 10.4% patients developing major depressive disorder and 11.9% patients are diagnosed as subsyndromal depression (22). Another retrospective cohort study evaluates the psychiatric status

of patients with hepatitis C treated by IFN-α and patients who stop the IFN-α treatment, their results exhibit that the incidence of depression and anxiety are notably elevated in patients treated by IFN-α compared with those stopping the IFN-α treatment (23). In our study, at W12 after the IFN-α treatment, we found that the HADS-Anxiety score and HADS-Depression score both increased after treatment and the percentages of patients had depression and anxiety evaluated by HADS were also elevated, which could be explained as follows: as a pro-inflammatory cytokine, IFN-α is illuminated to be able to lower the level of tryptophan (TRP), which is a precursor of serotonin, through inducing the TRP to transfer to kynurenine (KYN) (24-27). QoL is another aspect in the management of mRCC patients treated by IFN-α, however is not regularly assessed by clinical studies or trials. In a cohort study enrolls 21 mRCC

Table 7 Factors affecting the elevation of EORTC QLQ-C30 Scale-Symptoms score at week 12 (W12) compared to week 0 (W0) by logistic regression model analysis

Parameters	Univariate logistic regression			Multivariate logistic regression		
	P value	OR	95% CI	P value	OR	95% CI
Age	0.425	1.013	0.981–1.045	0.714	1.008	0.966–1.052
Gender (male)	0.284	0.664	0.314–1.404	0.507	0.735	0.296–1.823
Higher highest education	0.315	0.783	0.485–1.263	0.863	0.946	0.504–1.777
BMI	0.129	1.113	0.969–1.278	0.844	1.026	0.794–1.326
Overweight	0.021	2.342	1.136–4.825	0.209	2.394	0.613–9.343
Smoke	0.251	1.526	0.741–3.143	0.332	1.516	0.654–3.514
Drink	0.797	0.908	0.435–1.895	0.564	1.292	0.542–3.080
Hypertension	0.237	1.576	0.742–3.348	0.130	1.996	0.816–4.883
Hyperlipidemia	0.518	0.794	0.395–1.597	0.210	0.572	0.239–1.371
Diabetes	0.082	2.648	0.884–7.937	0.083	3.167	0.860–11.665
Higher ECOG performance	0.182	1.687	0.783–3.634	0.151	1.966	0.781–4.948
Histology (clear RCC *vs.* others)	0.291	0.612	0.246–1.523	0.428	0.659	0.235–1.847
Number of metastatic site (>1 *vs.* 1)	0.321	2.339	0.437–12.529	0.147	3.971	0.615–25.636
Metastatic site (lung *vs.* others)	0.333	0.682	0.314–1.481	0.271	0.582	0.222–1.526
Tumor size >7 cm	0.870	1.060	0.526–2.139	0.876	0.935	0.404–2.165
Prior radiotherapy	0.911	0.892	0.122–6.539	0.663	1.679	0.164–17.241
Prior chemotherapy	1.000	–	0.000	1.000	–	0.000

Data was presented as P value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting the elevation of EORTC QLQ-C30 Scale-Symptoms score at week 12 (W12) compared to week 0 (W0) were determined by univariate and multivariate logistic regression model analysis. Highest education was scored as: primary school or less =0, high school =1 and undergraduate or above =2. P value <0.05 was considered significant. EORTC QLQ-C30 Scale, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

patients treated by the combination of erythropoietin, IFN-α2a and interleukin (IL)-2, their results showed that the QoL assessed by Functional Assessment of Cancer Therapy scale of 10 patients is elevated after treatment (28). In our study, the EORTC QLQ-Global health status score, EORTC QLQ-Symptoms score and EORTC QLQ-Function score did not deteriorate throughout the whole course of treatment, indicating the QoL of mRCC patients in our study treated by IFN-α did not aggravated after treatment. This result in our study might be due to that the burden of disease relieved after treatment, and the EORTC QLQ-Function score was elevated at W12 and the EORTC QLQ-Symptoms score did not vary throughout the whole treatment course, which contributes to the unchanged score of EORTC QLQ-Global health status.

Despite that depression and anxiety of patients with

mRCC treated by IFN-α are occasionally reported, the effort of evaluating the predicting factor of this issue is still scarce. And in view that there might be difference of anxiety and depression in mRCC patients treated by IFN-α, exploring the predicting factors for the incidences of anxiety and depression might provide guidance for the patient selection in clinical practice. To our best knowledge, this is the first study to investigate predictive factors for the incidence of depression and anxiety in mRCC patients treated by IFN-α, and the majority of prior studies only focus on patients with hepatitis and other solid tumors (29-31). A prospective cohort study illustrates that severity of preexisting depressive symptoms and additional physical comorbidities predict early onset of depression, and additional physical comorbidities as well as depressive temperament associate with persistent depression in

hepatitis C (HCV) patients treated by IFN-α (29). And another cohort study elucidates that social support decreases the depression induced by low-dose IFN-α treatment in melanoma patients (31). The studies investigating the predictive value of baseline characteristics for depression and anxiety in cancer patients receiving IFN-α treatment are very rare. An earlier study conducted by Capuron *et al.* illustrates that RCC or malignant melanoma patients with higher Montgomery-Asberg depression rating scale (MADRS) scores at baseline present with moderate to severe depressive symptoms after IL-2 and/or IFN-alpha treatment, and baseline emotional symptoms, sleep disorders and low social support are predictors for depressive symptoms at the first month of IL-2 and/or IFN-alpha treatment (32). However, in their study, the sample size was small (N=32), and they included not only RCC patients but also malignant melanoma patients. In our study, older age, elevated level of highest education independently associated with less risk of HADS-Anxiety score elevation post treatment, while hypertension independently correlated with increased risk. As for depression, older age was also an independent predicting factor for reduced risk of increased HADS-Depression score. Those results in our study could be explained as follows: (I) older adults have stronger expectancy for a positive future compared with younger adults when they both have initial negative or ambiguous scenario, indicating the elderly might be less likely to develop depression and anxiety (33); (II) a higher education level is related to an obvious increase of self-assessed health level, life satisfaction and quality of life, which suggests a higher education level may reduce the risk of anxiety (34); (III) as to hypertension, it is elucidated to be highly correlated with symptoms of depression (35).

Accumulating studies confirm that QoL is another aspect crucial to cancer patients treated by IFN-α. A multicenter, open-label, prospective randomized phase III trial reports that the QoL are the same between resected melanoma patients treated by high dose IFN-α-2a and low dose IFN-α-2a (36). Nonetheless, there is still no study evaluating the predictive factors for QoL in mRCC patients treated by IFN-α, and the studies investigating the predicting value of baseline characteristics for the change of QoL in patients with other cancers treated by IFN-α are few, either. A study that is conducted earlier in 2002 elucidates that the toxicity of IFN-α-2b correlates with the change of QoL score in melanoma patients (37). In our study, the QoL was assessed by the EORTC QLQ-C30 Scale, and the multivariate logistic regressions revealed that smoke, hypertension,

diabetes and higher ECOG performance independently predict higher risk of EORTC QLQ-Global health status score reduction, and higher ECOG performance was also an independent predictive factor for reduced EORTC QLQ-Function score. In addition, no baseline characteristic was found to be correlated with the escalation of EORTC QLQ-Symptoms score. There are several probable explanations for our results: (I) smoking pejoratively affects the treatment response, survival and performance status in patients with various cancers, indicating smoking may decrease the QoL in patients by impairing the efficacy of treatments (38,39); (II) as to diabetes and hypertension, the symptoms such as dizziness, headache and fatigue caused by hypertension, and eating disorder, fatigue as well as emaciation resulted from diabetes, could notably decrease the QoL of cancer patients; (III) ECOG performance status illustrates the physical status of cancer patients aims to evaluate their tolerance to multiple treatments, a higher ECOG performance status suggests a more unsatisfactory physical condition and less tolerance to the treatments, which could result in a poorer QoL.

There were several limitations in this study: (I) our study was conducted in a single center that might result in a selection bias in our study; (II) the sample size was small; (III) the long-term evaluation of anxiety, depression and QoL in mRCC patients treated by IFN-α in our study were not assessed.

In conclusion, anxiety and depression increased while QoL did not deteriorate in mRCC patients during IFN-α treatment, and age, highest education, hypertension, smoke, diabetes as well as higher ECOG performance status correlated with their aggravation.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.11.07). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in

1472

Wang et al. Predictive factors for anxiety, depression and QoL in mRCC patients

accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital and conducted according to the Helsinki Declaration. The number of the Ethic Approval was KY2012-12. All patients provided written informed consents.

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