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Psychological states, serum markers and survival: associations and predictors of survival in patients with renal cell carcinoma

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Abstract

This study sought to determine if there was an association between prognostic-based serum biomarkers, survival, and psychosocial factors in patients with meta-static renal cell carcinoma. Associations were found between psychosocial factors and biomarker levels (hemoglobin with depressive symptoms ($r = -0.29$), positive affect ($r = 0.30$), social support ($r = 0.19$), and perceived stress ($r = -0.27$); albumin with depressive symptoms ($r = -0.19$), positive affect ($r = 0.22$), and social support ($r = 0.20$); alkaline phosphatase with depressive symptoms ($r = 0.21$), all p values < 0.05 . After adjustment for disease-related risk factors, only the associations between positive

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Human and Animal Rights and Informed Consent All procedures followed were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

affect and perceived stress with hemoglobin remained significant (p 's < 0.05). Positive affect (HR = 0.90; 95 % CI = 0.83, 0.97; p = 0.009) and depressive symptom total scores (HR = 1.03; 95 % CI = 1.01, 1.06; p = 0.013), and alkaline phosphatase (HR 2.72; 95 % CI = 1.41, 5.24; p = 0.003) were associated with survival. This study suggests that measures of positive and negative psychological outlook may contribute differently to health, well-being, and survival.

Keywords

Positive affect; Cancer; Depression; Biopsychosocial; Positive psychology; Survival

Introduction

The majority of research in health psychology has focused on patients' negative psychological states or traits after diagnosis of diseases, including cancer (Reiche et al. 2005; Thaker et al. 2006) however positive psychological states may also play a role in disease processes. For example, Shapiro (Shapiro et al. 2010) found that cancer takes its psychological toll not only by increasing levels of negative emotion but also by reducing positive affective experience. In other words, patients may not necessarily have an abundance of negative emotions, but rather they may have a lack of positive emotions that may not be solely related to the cancer experience. It follows that emotional states could be associated with biologic factors known to be significant prognostic factors in the cancer disease process, and further, positive affect may be just as an important of a factor to consider as the traditionally researched negative psychosocial variables (e.g., depression). There is extensive debate about whether positive and negative affect are independent of each other or are on a continuum. Indeed, it has been shown that mechanisms of positive and negative affect have distinct contributions to biologic processes such as blood pressure and heart rate (Ilies, Dimotakis, & Watson 2010), and to psychological processes such as creativity and perceived stress (Isen 1999; Watson 1988). However, little research has examined positive affect independent of negative affect in oncology and specifically in patients with renal cell carcinoma (RCC), and therefore the clinical relevance of positive affect has not been established.

Laboratory markers are routinely used to predict severity of disease and are often used as prognostic factors for survival in RCC patients. Research findings vary with respect to which factors consistently predict survival in patients with RCC (Mekhail et al. 2005; Motzer et al. 2002), however findings on routine preoperative laboratory studies may be more important predictors of survival than molecular proliferation markers (Lehmann et al. 2004). The risk categorization developed by Motzer et al. classifies RCC patients into prognostic risk groups on the basis of three factors: hemoglobin levels, corrected serum calcium levels, and Karnofsky performance status (KPS), although other biological markers also predict health status in RCC patients (Brookman-Amissah et al. 2009; Mekhail et al. 2005). One of these prognostic factors, hemoglobin levels, as well as other markers including serum albumin, and alkaline phosphatase are serum components that are commonly evaluated in patients with RCC and are also associated with clinical outcomes.

These serum components can also be sensitive to psychosocial factors. For example, Mal'tsev found that hemoglobin levels (an index of oxygen transportation in red blood cells) were lower in subjects who reported higher stress (Mal'tsev et al. 2010). Researchers have also reported that albumin and alkaline phosphatase are susceptible to emotional states (Abel 1993; Koplik et al. 2002), and that even transient environmental events can influence these biomarkers. For example, Matsunaga (Matsunaga et al. 2009) found that after healthy couples hugged and kissed, not only did they report an increase in positive affect, but serum albumin levels increased, while feelings of irritation were negatively correlated with serum albumin levels (Matsunaga et al. 2009). The presence of elevated alkaline phosphatase (ALP) has been found to be a significant independent prognostic factor in progression-free survival in RCC, can indicate bone metastases (Lee et al. 2006; Saif et al. 2005), and has been shown to increase during times of stress (Abel 1993).

Based on the potential relevance of laboratory markers in RCC progression and the potential influence of emotional states on specific serum variables, we evaluated the association between psychosocial factors and hemoglobin, serum albumin, and alkaline phosphatase levels. In addition, RCC is an immunogenic disease (Tang et al. 2013) and associations between psychosocial factors and survival would be more apparent for RCC than other cancers. We recruited patients with metastatic RCC (mRCC) to explore the association between psychological factors and serum-based prognostic markers and predictors of survival and hypothesized that there would be an association between psychological and biological outcomes such that positive psychological variables would be associated with a better prognostic profile and negative psychological variables with a worse prognostic profile and that psychological factors would be associated with survival, independent of risk status.

Methods

Patients

Patients with mRCC who had a life expectancy of at least 24 months and a Zubrod performance status (Oken et al. 1982) of 2, aged 18 years and above, with the absence of any intercurrent illness, were recruited from the genitourinary medical oncology and urology clinics at The University of Texas MD Anderson Cancer Center between April 2000 and November 2005. Participants in this study had stage IV cancer, meaning the cancer had spread to other organs or lymph nodes where average survival time ranges from 4 months to 5 years, with 8 % expected to live 5 years, depending on cancer type (clear cell, sarcomatoid, papillary) and treatment (chemotherapy, full nephrectomy, partial nephrectomy, etc.) (Dutcher & Nanus 2011; Pace et al. 2013; American Cancer Society 2012). Informed consent was obtained from each participant prior to enrollment in the study. Patients completed assessments of psychosocial and quality-of-life variables and blood samples were drawn to measure serum markers of disease. Blood serum has been shown to undergo changes after chemotherapy treatment (Winter et al. 2013), so patients who had undergone chemotherapy were excluded from our analysis because of the potential impact of the medications on serum markers. The present study was a part of a larger study investigating the association between psychological factors and survival (Cohen et al. 2012). The study

was approved by the Surveillance Committee for the Protection of Human Subjects at MD Anderson.

Measures

Psychosocial variables examined included depressive symptoms, positive affect, social support, and perceived stress. Symptoms of depression were measured using the Centers for Epidemiologic Studies-Depression (CES-D) assessment (Radloff 1977). The CES-D is a well-validated, 20-item, self-reported measure of depressive symptoms that focuses on affective components of depression, with scores of 16 or above classified as meeting screening criteria for depressive symptoms with further evaluation recommended. Internal consistency is high in the general population, and in our study the Cronbach α was 0.92.

Additionally, the CES-D has a subscale of 4 positively worded questions that are often used as a measure of positive affect (Blazer 2004; Fowler & Christakis 2008; Moskowitz 2003; Pressman & Cohen 2005). We used these four questions to assess positive affect levels. The reliability of the four item scale in our study was high ($\alpha = 0.85$). The positive affect subscale and CES-D scores without that subscale were correlated at -0.56 ($p < 0.001$), indicating that although the scales are statistically significantly associated, aspects of what these two scales are measuring are also distinct.

The 11-item version of the Duke Social Support Index (DSSI) assessed levels of social support. The DSSI assesses two major components of social support: social network and subjective support (Koenig et al. 1993).

Perceived stress was measured using the Perceived Stress Scale (PSS) (Cohen et al. 1983), which measures perceptions of ongoing stress.

Patient demographic information (age, gender, ethnicity) as well as clinical information (date of diagnosis, type of treatment, number and location of metastases, Karnofsky performance status, and corrected calcium) was extracted from patient charts after the completion of initial study requirements. Serum components examined for this study included hemoglobin, serum albumin, and alkaline phosphatase.

Patients were classified into prognostic risk groups (low, intermediate, and high) on the basis of the following factors: KPS <80 %; corrected calcium >10 mg/dl; and serum hemoglobin <13 mg/dl for males and <11.5 mg/dl for females, (Motzer et al. 2002). Those with zero or one risk factor were classified at low risk, those with two risk factors were classified at intermediate risk, and those with three risk factors were classified at high risk. Hemoglobin was the only variable included in the psychosocial/serum analysis and the determination of risk group.

Analysis

Pearson correlational analyses and linear regression analyses were performed to determine associations between psychosocial factors and biomarkers. Correlation coefficients were computed among eight variables, including the psychosocial variables of depressive symptoms (with and without the positive affect questions included), positive affect, social

support, and perceived stress and the bio-marker variables of serum hemoglobin, albumin, and alkaline phosphatase. The association between all variables and RCC risk group was assessed using analysis of variance. Linear regression analyses were then conducted to examine the association between the psychosocial variables and biomarkers when controlling for RCC risk group. A p value of < 0.05 was considered statistically significant. Tolerance and variance inflation factor values were examined and did not indicate problematic levels of multicollinearity among the explanatory variables included in the final regression models, including the models that entered CES-D without the positive affect variables and the positive affect subscale scores.

As hemoglobin is a variable that in part determines risk factor and is also an outcome measure, we conducted additional analyses excluding hemoglobin in the risk group determination. This was only done for the analyses where the outcome was hemoglobin level.

We analyzed the serum biomarkers and psychosocial factors as predictors of survival using Cox regression models where a p value < 0.05 was considered statistically significant. The Kaplan–Meier plots were applied to compare the difference in survival time by the dichotomized groups for depressive symptoms and positive affect. We used the date of diagnosis of metastatic disease to determine survival versus initial diagnosis as mortality is commonly associated with the metastasis of disease. In order to have the alkaline phosphatase data normally distributed, alkaline phosphatase raw score levels were log-transformed. Lastly, in order to examine the joint effects of positive affect and depressive symptoms (CES-D without positive affect items) on survival patients were grouped using median splits into four categories: high positive affect/low depressive symptoms; low positive affect/low depressive symptoms; high positive affect/high depressive symptoms; and low positive affect/high depressive symptoms, and the same survival analyses as described above were conducted. For all analyses we included RCC risk factor classified as low, intermediate, or high risk.

Results

Clinical, demographic, and psychosocial data were collected from 217 patients. Of the 217 participants, 145 did not undergo prior chemotherapy and were potentially evaluated in this study. However data were missing for some variables and therefore none of the analyses included more than 138 patients. The average age of participants was 60 years (range, 28–83 years); 106 (73 %) were male. Eighty-two patients (64 %) were classified in the low-risk group; 36 (28 %) were classified in the intermediate-risk risk group; and 13 (10 %) were classified in the high-risk group (Table 1). At the time of analysis, 55.2 % of patients were deceased. For those who had died, the average time from diagnosis of metastatic disease to death was 2 years (SD = 1.9, range 0.36–13.5 years). Mean CES-D total scores were 10.3 (7.8), with 22 % of the population scoring 16 or above.

We first conducted correlational analyses which revealed significant associations between the psychosocial variables and biomarker outcomes (Table 1). Depressive symptoms (CES-D total) and perceived stress were negatively correlated with hemoglobin levels, and positive

affect and social support were positively correlated with hemoglobin levels. Depressive symptoms were also negatively correlated with albumin and positive affect and social support positively correlated with albumin. Lastly, only depressive symptoms were positively correlated with alkaline phosphatase (Table 1).

We then conducted ANOVAs, using the Tukey posthoc analysis for group comparisons, to determine if there was an association between RCC risk group (low, intermediate, or high) and all psychological and serum marker outcomes. Analyses revealed risk group differences between the high and low groups for all psychosocial variables ($p < 0.05$), where the high risk group reported the worst outcomes, with the exception of social support for which there were no risk group differences (Table 2). There were no differences between the intermediate and high or intermediate and low risk groups for the psychosocial measures. Examination of serum biomarkers and risk group revealed differences between all three risk groups for hemoglobin and albumin and differences between the high and low risk groups and intermediate and low ($p < 0.01$) (Table 2).

Linear regression analyses, controlling for RCC risk group, revealed that only positive affect and perceived stress remained significantly associated with hemoglobin levels. However, none of the other psychosocial factors, including total CES-D scores and CES-D scores without the positive affect subscale, were significantly correlated with the biomarkers. After controlling for risk group, none of the psychosocial factors remained associated with albumin or alkaline phosphatase levels (Table 3).

As hemoglobin was simultaneously an outcome variable and one of the factors that determined clinical risk status, we conducted the analyses where hemoglobin was the outcome variable excluding hemoglobin from the risk group. With the creation of this new variable, 30 participants in the medium risk group moved to the low risk group, and 13 participants in the high risk group moved to the medium risk group. The association between positive affect ($B = 0.15$, $p = 0.004$) and hemoglobin and perceived stress ($B = -0.05$, $p = 0.004$) and hemoglobin remained significant, and there was also a negative association between CES-D total score ($B = -0.05$, $p = 0.014$), CES-D without positive affect ($B = -0.05$, $p = 0.038$), with hemoglobin levels. No other associations were statistically significant using the two risk factor model.

To determine whether positive affect would remain associated with hemoglobin independent of depressive symptoms, a subsequent multiple regression analysis was conducted with three predictors entered simultaneously into the analysis: CES-D without the positive affect variables, positive affect scale, and risk group. The overall variance explained for hemoglobin levels by the predictors was 57 %. Of the three predictors, risk group ($B = -0.71$, $p < 0.001$) and positive affect ($B = 0.16$, $p = 0.027$) remained associated with hemoglobin levels, however CES-D without the positive affect variables was no longer associated with hemoglobin levels ($B = 0.02$, $p = 0.74$).

We examined whether the psychosocial variables and serum markers were associated with survival from date of onset of metastatic disease (Table 4). Survival analyses found that when controlling for risk group, both CES-D total ($HR = 1.85$; 95 % $CI = 1.07, 3.20$; $p =$

0.030) and positive affect (HR = 0.90; 95 % CI = 0.83, 0.97; $p = 0.009$) were associated with survival; however the positive affect subscale had a stronger association with survival than CES-D total scores. CES-D without the positive affect variables was not associated with survival ($p = 0.06$). Of the biological variables assessed, only alkaline phosphatase was significantly associated with survival (HR 2.72; 95 % CI = 1.41, 5.24; $p = 0.003$). In joint analysis of positive affect and CES-D scores without the positive affect items, controlling for risk factors, patients with high levels of positive affect and low levels of depressive symptoms had a 50 % reduced risk of death than those who had low positive affect and high depressive symptoms (HR = 0.50; 95 % CI = 0.27, 0.92; $p = 0.026$). Patients low in positive affect and low in depressive symptoms or high in positive affect and high in depressive symptoms had better survival outcomes than those low in positive affect and high in depressive symptoms, but those differences were not significantly different (Fig. 1).

Discussion

In our primary analysis, we found that in patients with mRCC, psychosocial factors were associated with serum biomarkers that are important to the patient's current health status. This is especially relevant as our study and other research has demonstrated that these same biomarkers are associated with survival (Brookman-Amisshah et al. 2009). Our analysis revealed a positive association between patient-reported positive affect and serum levels of hemoglobin and a negative association between perceived stress and serum levels of hemoglobin, even after controlling for RCC risk group. Importantly, the association between positive affect and hemoglobin levels remained significant even after controlling for depressive symptoms, suggesting that aspects of positive affect contribute distinctly and independently from negative affect. Although depressive symptoms and social support were each associated with serum biomarker levels in univariate analyses, these associations were no longer significant after controlling for RCC risk group. When examining the alternate classification for risk group that removed hemoglobin as a factor, measures of negative affect were negatively associated with hemoglobin levels while positive affect was positively associated with hemoglobin levels. None of the psychosocial variables were associated with alkaline phosphatase or albumin levels after controlling for RCC risk group.

Positive affect was also associated with a 10 % reduction in mortality, with no significant association for survival for the depressive symptom items alone, even after controlling for disease severity, which was associated with positive affect and depressive symptoms. Survival outcomes were substantially better for patients who reported both high positive affect and low depressive symptoms, with a 50 % reduction in mortality relative to patients reporting low positive affect and high depressive symptoms, even after controlling for risk group. The alternative combinations of positive affect and depressive symptoms fell in between, yet were not statistically significant.

In a previous report that included these patients as well as those who had prior chemotherapy, we found that increased levels of depressive symptoms and a blunting of the cortisol slope were both associated with decreased survival (Cohen et al. 2012). Consistent with those results, the present study on the subsample of patients revealed that not only was there an association between biological and psychological variables, but that the main factor

driving the association between survival and depressive symptoms, as assessed from the CES-D, was the positive affect items. Moreover, survival outcomes were significantly improved for patients reporting high levels of positive affect and low levels of depressive symptoms, regardless of disease severity.

Positive psychological states have been independently associated with different biological outcomes such as increases in immunoglobulin A (Watanuki & Kim 2005), and a decrease in interleukin-6 (IL-6) and other inflammatory cytokines, cortisol, and fibrinogen to name a few (Ryff et al. 2004; Steptoe & Wardle 2005). Specifically, c-reactive protein, cortisol, and plasma interleukin-6 have been shown to be inversely associated with positive affect, and the association remained significant after controlling for negative affect, suggesting that the association was not secondary to the absence of depression (Ryff et al. 2004). Our study results are consistent with other research examining psychological states and indices of health that have found a link between psychological symptoms and disease (Reiche et al. 2004; Satin JR 2010; Spiegel & Giese-Davis 2003), and a smaller but still substantial body of work that demonstrates a link between positive affect and disease, such that positive affective states could be considered protective (Steptoe & Wardle 2005; Strand EB 2006).

Our finding that depressive symptoms alone were not significantly associated with serum markers after controlling for disease risk is surprising considering the reported role of depression in the disease process and extensive research linking depression to biological processes. For example, depression has been linked to changes in IL-6, an inflammatory marker that has prognostic value for cancer patients (Jehn et al. 2006; Lutgendorf et al. 2008; Sephton et al. 2009), and depression has also been shown to be significantly related to other biological outcomes in cancer (Reiche et al. 2005; Sharma et al. 2008). Differences between this study's findings and previous studies that may explain the lack of association between depression and serum markers may be that all patients in the current study had stage IV disease; patients had not yet experienced the side effects of chemotherapy; or that other factors such as whether or not supportive care needs were being met could affect the perception and hence reporting of psychological distress.

Mechanisms of psychobiological effects are not known in health outcomes, however researchers report that there may be predisposition traits leading to reported positive affect that are dynamic, such that experienced happiness over time may be more important than overall life satisfaction (Kahneman et al. 2006). Therefore, the overall experience of positive affect versus feelings of depressive symptoms and stress could have implications for well-being (Diener et al. 2006). Separately, these processes may be associated with distinct disease outcomes therefore confirming the importance of expanding research to include processes that may be protective as well as those that may augment the disease process. The clinical challenge is then that comprehensive treatment would involve not only minimizing negative psychological states but incorporating interventions to improve positive psychological states.

This study is limited by the fact that while we demonstrated an association between the psychological and biological, more research is needed to explore causality. For example, aspects of metastatic disease progression may influence a person's ability to be happy or

inversely positive affect could influence the disease process. The current design cannot disentangle the true direction of the effect; however, associations did remain after controlling for disease factors. Additionally, in our statistical model the R value was higher (0.75), indicating a stronger correlation, when the predictor was positive affect and the dependent variable was hemoglobin than when hemoglobin was the predictor and positive affect was the dependent variable (0.31). Personality traits such as optimism may underlie the experience of positive affect, which may be better measured as a separate construct. Although the CES-D has demonstrated appropriate psychometric properties, the items used to measure positive affect in our study were a subscale of the CES-D so consequently there may be more in depth measurements that could better decipher specifics about the nature of positive affect as it relates to bio-markers. However empirical evidence has demonstrated support for the distinct constructs of positive and negative affect as measured by the CES-D (Blazer 2004; Pressman & Cohen 2005; Radloff 1977; Sheehan et al. 1995). It may be that there are measurable serum differences between patients who report intense joy versus those who report general contentment. However, our findings are consistent with other research that has suggested that independent psychological variables predict 'distinct' biological correlates, or more simply stated, well-being correlates with healthier biological states (Ryff et al. 2006). Finally, the predominance of males in our study population could have affected our outcomes, as it has been shown that there are gender effects in physiological and psychological responses to stress (Ferraro & Nuriddin 2006), as well as in reporting perceived stress (Marinaccio et al. 2013), where males are less likely to experience psychological distress and can have less negative perceptions of stressors than women. Considering the other limitations of this study, our findings should be interpreted with caution and confirmed through future longitudinal research.

Although identifying biomarkers of disease is important and imperative to treatment, biopsychosocial models of disease posit that psychological variables are also important predictors of disease outcome (Antoni et al. 2006). Our findings contribute to our understanding of mechanisms that may be important in the progression of mRCC. The present data suggest not only that there is also an association between positive psychological variables and markers of disease progression, but that positive affect may be a distinct construct that may be just as important as the more commonly studied negative psychological variables. The sources of positive affect and its benefit in cancer populations remain a significant area for future research.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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Abbreviations

mRCC	Metastatic renal cell carcinoma
RCC	Renal cell carcinoma
CES-D	Centers for Epidemiologic Studies-Depression
PSS	Perceived Stress Scale
DSSI	Duke Social Support Index

Fig. 1. Kaplan–Meier survival curves examining the joint effect of positive affect and depressive symptoms

Table 1
Pearson correlational analysis of associations between psychosocial measures and biomarkers

Psychosocial variable	Hemoglobin	Albumin	Alkaline phosphatase
CES-D total			
r	−0.29	−0.19	0.21
p	0.000	0.031	0.018
n	138	127	130
Positive affect			
r	0.30	0.22	−0.16
p	0.000	0.013	0.070
n	138	127	130
Social support			
r	0.19	0.20	−0.13
p	0.033	0.021	0.15
n	139	128	131
Perceived stress			
r	−0.27	−0.15	0.12
p	0.002	0.11	0.18
n	130	121	124

Depressive symptoms were measured using the Centers for Epidemiologic Studies-Depression assessment (CES-D), positive affect using a four-item subscale of the CES-D, social support using the Duke Social Support Index (DSSI), and perceived stress using the Perceived Stress Scale (PSS)

Results of analysis of variance between risk group and serum markers and psychosocial variables**Table 2**

Variable	Risk group	Mean	SD	F	p value
CES-D				6.6	0.002
	High risk	16.4 ^a	10.6		
	Intermediate risk	11.3	8.2		
	Low risk	8.6 ^b	6.6		
CES-D w/o positive affect				4.2	0.018
	High risk	10.9 ^a	7.9		
	Intermediate risk	7.9	6		
	Low risk	6.2 ^b	5.2		
Positive affect				4.2	0.017
	High risk	7.3 ^a	3.7		
	Intermediate risk	8.6	2.6		
	Low risk	9.5 ^b	2.7		
Social support				1.8	0.17
	High risk	32.3	9.1		
	Intermediate risk	35.2	9.9		
	Low risk	40.5	21.5		
Perceived stress				4.6	0.012
	High risk	23.9 ^a	12.3		
	Intermediate risk	18.7	8.8		
	Low risk	16.5 ^b	6.9		
Hemoglobin				77	<0.001
	High risk	10.6 ^a	1.5		
	Intermediate risk	11.9 ^b	1.4		
	Low risk	14.2 ^c	1.1		
Albumin				32	<0.001
	High risk	3.3 ^a	0.5		
	Intermediate risk	3.9 ^b	0.4		
	Low risk	4.2 ^c	0.3		

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Variable	Risk group	Mean	SD	F	p value
Alkaline phosphatase	High risk	173.3 ^a	154.3	8.5	<0.001
	Intermediate risk	110.3 ^b	38		
	Low risk	95 ^c	46.2		

Different letter superscripts indicate groups are significantly different from each other $p < 0.05$. Depressive symptoms were measured using the Centers for Epidemiologic Studies-Depression assessment (CES-D). Positive affect using a four-item subscale of the CES-D, social support using the Duke Social Support Index (DSSI), and perceived stress using the Perceived Stress Scale (PSS)

Table 3
Results of linear regression analyses of associations between psychosocial variables and serum biomarkers, controlling for renal cell carcinoma risk group

Variable	Parameter estimate	Standard error	<i>p</i> value
Hemoglobin			
High risk group	−3.47	0.39	<0.0001
Intermediate risk group	−2.33	0.26	<0.0001
CES-D total	−0.02	0.01	0.22
CES-D w/o positive affect	−0.02	0.02	0.33
Positive affect	0.09	0.04	0.020
Social support	0.006	0.006	0.31
Perceived stress	−0.03	0.01	0.040
Alkaline phosphatase			
High risk group	0.35	0.13	0.006
Intermediate risk group	0.16	0.08	0.050
CES-D total	0.007	0.005	0.15
CES-D w/o positive affect	0.007	0.006	0.31
Positive affect	−0.01	0.01	0.34
Social support	−0.002	0.002	0.36
Perceived stress	0.001	0.005	0.74
Albumin			
High risk group	−0.87	0.12	<0.0001
Intermediate risk group	−0.29	0.08	<0.0001
CES-D total	−0.0008	0.005	0.86
CES-D w/o positive affect	0.0001	0.006	0.98
Positive affect	0.01	0.01	0.29
Social support	0.003	0.002	0.11
Perceived stress	0.0004	0.004	0.94

Depressive symptoms were measured using the Centers for Epidemiologic Studies-Depression (CES-D) assessment, Positive affect using a 4-item subscale of the CES-D, social support using the Duke Social Support Index, and perceived stress using the Perceived Stress Scale

Table 4
Cox regression models for survival from the diagnoses with metastatic disease

Variable	Parameter estimate mean (SE)	Hazard ratio	95 % CI	<i>p</i> value
Risk group				
High risk	1.76 (0.35)	5.82	(2.91, 11.64)	<0.0001
Intermediate risk	−0.23 (0.30)	0.80	(0.44, 1.44)	0.45
CES-D total	0.04 (0.01)	1.03	(1.01, 1.06)	0.013
CES-D w/o positive affect	0.04 (0.02)	1.04	(1.00, 1.08)	0.06
Positive affect	−0.11 (0.04)	0.90	(0.83, 0.97)	0.009
Alkaline phosphatase	0.99 (0.34)	2.72	(1.42, 5.24)	0.003

SE standard error; positive affect using a 4-item subscale of the CES-D; Cox regression included risk group in each model