PROSPECTIVE ANALYSIS OF STRESS AND IMMUNITY IN ADVANCED CANCER

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ABSTRACT

Objectives: The aims of this study were to assess chronic stress in a sample of advanced cancer patients, test the association between stress and NK cell immune markers over time, and examine whether stress predicts immune markers over time.

Methods: A sample of 99 patients were recruited for the study. Patient inclusion criteria were biopsy, radiological, or biological evidence of advanced cancer. Stress was analyzed using the Perceived Stress Scale and immunity was assessed using CD16+ and CD56+ lymphocyte subsets. . Descripitve statistics, Mann-Whitney U tests, and cross-lagged panel analyses were used to test the aims.

Results: Mean stress levels were not higher than the general population. Using Mann Whitney U tests, significant differences in CD16 and CD56 were observed between high stress and low stress groups at several time points. Cross-lagged panel analyses also showed that stress predicted abnormal levels of CD16 and CD56s at subsequent time points.

Conclusion: Although stress levels among participants was not higher than the general population, for those patients who reported higher levels of stress Mann-Whitney U tests and cross-lagged panel analyses suggested that stress was associated with dysregulation of both CD16+ and CD56+. This dysregulation could decrease the body's defenses to identify and destroy new tumor cells and contribute to the growth of the primary tumor or metastatic spread of the disease. Clinical applications of this study should involve developing interventions that are designed to lower stress in patients with cancer.

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INTRODUCTION

The unpredictable and uncontrollable course of cancer makes it a particularly stressful life experience. Cancer is a life changing event associated with high levels of psychological stress and is one of the leading causes of death worldwide (Sehlen et al., 2003) (Jemal, Siegel, Xu, & Ward, 2010). In 2010, 1,529,560 people were diagnosed with cancer in the United States and 569,490 died from this disease (Jemal, et al., 2010). The highest rates of psychological stress are reported by patients at advanced stages of disease, or when the cancer recurs or spreads metastatically (Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Zambora and colleagues found the highest levels of distress among patients diagnosed with lung, pancreatic, and liver cancer. It is likely that higher rates of stress associated with these diagnoses reflect their poor prognosis and limited number of effective cancer therapies for those sites (Yan & Sellick, 2004; Zabora, et al., 2001).

Cella and colleagues proposed that cancer recurrence is a traumatic event that places individuals at greater risk for a stress response (Cella, Mahon, & Donovan, 1990). These investigators observed that patients with cancer rated the recurrence as more problematic than the adjustment to the initial diagnosis (Cella, et al., 1990). Similarly, Andersen and colleagues found in a sample of women diagnosed with breast cancer that those who experienced a recurrence reported higher levels of stress than those who did not (Barbara L. Andersen, Shapiro, Farrar, Crespin, & Wells-DiGregorio, 2005). Metastatic spread, which can be a recurrenceor present at the time of the initial diagnosis, has also been associated with higher levels of stress among cancer patients secondary to the poor prognosis that often accompanies metastatic spread (Sehlen, et al., 2003).

Stress is proposed to result when the demands being placed on an individual are considered to be threatening or harmful and exceed the resources available to handle the burdens (Maddock &

Pariante, 2001). At these times, individuals perceive the situation as uncontrollable, unpredictable and/or overloaded (S. Cohen, 1988). Chronic stress may be characterized by persistent demands that are equal to or longer in duration than 1 month. Chronic stress has been found to result in the dysregulation of multiple immune functions, including components of the innate immune system that may play a role in protecting against the spread of cancer (Segerstrom & Miller, 2004).

Andersen's biobehavioral model of cancer provides a comprehensive framework that conceptually links heightened psychological stress to cancer progression (B. L. Andersen, Kiecolt-Glaser, & Glaser, 1994). The model proposes that biological and behavioral responses to stress result in the modulation of immune components that increase risk for disease progression. Although evidence has been found for the link between stress and immunity and immunity and disease progression (Kiecolt-Glaser & Glaser, 1999; Segerstrom & Miller, 2004), to date evidence for this model has focused on demonstrating an association between stress and immune modulation and between immune function and disease progression (Figure 1).

A number of studies have examined the association of stress with immune components that play a role in protecting against the spread of cancer. Much of this literature has focused on the number and function of Natural Killer (NK) cells. NK cells are a component of the innate immune system. They are able to detect and destroy altered self cells, such as tumor or virally-infected cells. These cells combat certain viral or bacterial infections, and also are involved in cytotoxicity of tumor cells (Vivier, Tomasello, Baratin, Walzer, & Ugolini, 2008). In a meta-analytic review of the literature examining association of stress with immune function, Segerstrom and Miller found consistent evidence that shows chronic stress was associated with a decrease in the number of NK cells in peripheral circulation and a down-regulation of their cytotoxic function (Segerstrom & Miller, 2004). For example, Cohen and colleagues showed that NK cell numbers were lower in unemployed subjects when compared to

employed subjects, with job status serving as a chronic stressor (F. Cohen et al., 2007). In addition, De Gucht and colleagues observed that nurses who reported higher stress levels had decreased percentages of the NK cells (De Gucht, Fischler, & Demanet, 1999). Similarly, stress in atopic individuals as measured by the Perceived Stress Scale was found to be negatively associated with decrements in NK cell numbers (Hoglund et al., 2006).

Specific to cancer, analogous results have been observed. These findings are important because NK cells play a key role in tumor cell surveillance and eradicating tumor cells (Souberbielle, 1994). Stress may decrease the ability of NK cells to effectively eliminate tumor cells. In a study of breast cancer patients, those who reported chronic stress had fewer NK cells than did to controls (Neises et al., 1995). Also, Levy and colleagues found that patients diagnosed with cancer who reported greater stress had lower NK cell activity (Levy, Herberman, Lippman, & d'Angelo, 1987). Similarly, Fawzy and colleagues also showed that participation in an intervention that decreased levels of stress among a sample with malignant carcinoma resulted in a significant increase of NK cells and NK cell activity (Fawzy et al., 1990). Thus, stress levels in cancer populations vary and can be changed but increased stress levels may adversely affect immune system function.

Others have shown that chronic stress is associated with a reduction in NK cell activity, which may or may not be a direct result of reduced cell numbers. For example Kiecolt-Glaser and Glaser showed that stress is associated with a downregulation of NK cell activity, which they hypothesized could lead to poor monitoring of the abnormal cells observed in cancer (Kiecolt-Glaser & Glaser, 1999). NK cell numbers and activity are critical in tumor immunosurveillance across several cancer types (Ghiringhelli, Ménard, Martin, & Zitvogel, 2006). Furthermore, Whiteside and Herberman suggested that NK cells are not only involved in surveillance and control of the spread of malignant cells, but also play a role in the elimination of established solid tissue metastases (Whiteside & Herberman, 1995).

In order to clarify some of the previous findings, this prospective study had several aims. First, we aimed to assess the prevalence of chronic stress in a sample of advanced cancer patients (e.g., patients with a diagnosis of primary liver or bile duct cancer, patients diagnosed with other cancer types with metastatic spread to the liver). We predicted that these patients would report higher levels of stress when compared to the general population. Second, we aimed to explore whether higher stress levels related to lower NK cell absolute numbers and percentages in this population. Third, we aimed to explore the longitudinal relationship between stress and NK cell number. Based on the literature, we expected for higher stress at earlier time points to be associated with abnormally low NK cell absolute numbers and percentages at subsequent time points among a sample of cancer patients.

METHODS

Design

The study was a prospective design. Both stress and blood samples were assessed prior to the participants' first treatment and then every 2 months for 6 months.

Participants

Ninety-nine patients diagnosed with advanced cancer were enrolled in the current study between January 2007 and October 2010. Patient inclusion criteria were: (1) biopsy, radiological, and/or biological evidence of primary liver or bile duct cancer or colorectal, ovarian, or breast cancer with liver metastases; (2) age 18 years or older; and (3) fluency in English. Exclusion criteria included: (1) current suicidal or homicidal ideation; or (2) current psychosis or thought disorder.

Instruments: Stress

Participants completed the Perceived Stress Scale at each assessment time point. The Perceived Stress Scale (PSS) is a 14-item questionnaire that measures the extent to which individuals appraise the events of their life as stressful in the last month. The questions in the PSS inquire about thoughts and feelings present during the past month, with answer choices including: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often. Scores can range between 0 and 56. For comparison, Cohen has found that an average individual in the United States would score below 20 (S. Cohen, 1988). A high level of stress for the purposes of this study was defined as a score of 27 or above on this PSS (1 standard deviation above the mean of the general population according to the Cohen standardization sample (S. Cohen, 1988)). The reliability and validity of this instrument has been tested, and the internal consistency has been demonstrated to range between .84 and .86 (S. Cohen, 1988).

Instruments: Immunity

The lymphocyte subsets chosen for analysis were CD16+ and CD56+. Blood draws were performed between the hours of 8:00am and 12:00pm, in order to control for differences in circadian rhythms on proposed immune system parameters. The University of Pittsburgh Cancer Institute's Immunologic Monitoring Laboratory uses standardized and validated assays, standard operating procedures, healthy donor controls, and biostatistical input, all of which reduces concerns regarding procedural-based variations. A complete blood count was also conducted. The absolute number and the percentage of NK cells (as measured with the CD16+ and CD56+ lymphocyte subsets) were determined by a single-platform flow cytometry-based method. Whole blood was used for staining of NK cells with fluorochrome-labeled monoclonal antibodies. Following lysis of the erythrocytes and the addition of sizing beads, NK cells were enumerated in a Coulter FC500 flow cytometer. Patient results

were compared to the results of healthy donor controls to determine if lymphocyte subsets were in the normal range.

Procedure

After receiving IRB approval, patients from a large tertiary cancer center that evaluates and treats patients with advanced cancer were approached for participation by one of four oncologists (TCG, JWM, DAG, AT). Patients who met the inclusion and exclusion criteria and were interested in speaking to a study team member about participation were then provided with information regarding the risks and benefits of the study. If the patient agreed to participate and provided written informed consent, s/he was interviewed by trained telephone examiners. The time-frame for the interviews was once prior to their first treatment and then every 2 months for 6 months.

Data Analyses

The data were entered into PASW version 18 (Chicago, IL) and verified. Descriptive statistics were performed including tests of normality. Chi-square analyses were performed for categorical variables and the non-normally distributed continuous data were analyzed using Mann-Whitney U tests. Lastly, cross-lagged panel analyses were performed to test the link between stress and immune system parameters over time.

RESULTS

Sociodemographic and Disease-Specific Characteristics of Sample

Of the 99 patients enrolled in the study, the mean age of the participants was 62 years and the majority were male (73.8%). More patients had hepatocellular carcinoma (72.7%) than other types of cancer; less common diagnoses included colorectal cancer (7.9%), cholangiocarcinoma (5.0%), and other

types of cancer (breast or ovarian) that had metastasized to the liver (14.4%). The mean number of lesions was 3.4, with a range from 3-10 lesions. The average size of the largest lesion was 6.2 cm, and 81.4% of participants had cirrhosis present. At baseline (prior to any treatment), 99 participants were available for analyses. At 2-months follow up, this number had dropped to 67 due to death or inability to complete the PSS questionnaires. At 4-months follow up the sample size was 48, and at 6-months follow up the sample remaining with complete data at all time points was 40 participants. At 6-months follow up, 47 participants (48% of the sample) had died.

Prevalence of Chronic Stress

Reports of chronic stress decreased among this sample from baseline to the 6-months follow up. At baseline, 27.3% of the participants had a PSS score of 27 or higher. At 2-months follow up this percentage was 22.4 and at 4- and 6-months follow-up high stress was 18.8% and 7.5% respectively. The mean and standard deviation of the PSS scores at each measurement are displayed in Table 1.

Between Group Differences in regard to Stress and Natural Killer Cell

Using Mann Whitney U tests, the differences in CD16+ and CD56+ were tested between patients with a PSS score < 27 and > 27. Significant differences between groups were observed at 4-months for percentage of CD16+ (Mann Whitney U=16.5, p=.01) and percentage of CD56+ (Mann Whitney U=14.0, p=.01) (Figures 2-3).

In addition, significant differences between PSS < 27 and > 27 were observed in regard to absolute numbers of CD16+ at baseline (Mann-Whitney U=237.50, p=.02) and 2-months follow up (Mann-Whitney U=79.0, p=.04). A significant difference between groups was also observed in regard to absolute numbers of CD56+ at baseline (Mann-Whitney U=258.50, p=.02), and at 4-months follow up (Mann-Whitney U=23.5, p=.05) (Figures 4-5).

Prospective Analyses of Stress and Natural Killer Cells

Using cross-lagged panel analyses, a trend towards significance was observed in which higher stress levels at 2-months predicted percent CD16+ in the high abnormal range at 4 months (OR=1.06, p<.10). Higher stress levels at 4-months significantly predicted percentages of CD16+ in the low abnormal range at 6-months (OR=.74, p<0.001). At 4-months, 64% of the variance of percent CD16+ was accounted for by stress and CD16+ at 2-months. Ninety-six percent of the variance of percent CD16+ at 6-months was accounted for by stress and CD16+ at 4-months (See Figure 6).

A trend towards significance was observed in which percent CD56+ at baseline predicted higher stress levels at 2-months (OR=2.46, p<.10). Higher stress levels at 2-months predicted percent CD56+ in the high abnormal range at 4-months (OR=1.07, p=.05). Finally, a trend toward significance was observed in that higher stress levels at 4-months predicted percent CD56+ in the low abnormal range at 6-months follow up (OR=.95, p<.10). Fifty-three percent of the variance of stress at two months was accounted for by stress and percent CD56+ at baseline. At 4-months, 49% of the variance of percent CD56+ was accounted for by stress and percent CD56+ at 2-months. Thirty percent of the variance of percent CD56+ at 6-months was accounted for by stress and percent CD56+ at 4-months (See Figure 7).

DISCUSSION

This study examined the effects of stress and immune system dysregulation in patients with advanced cancer. The investigation is one of few studies that included a prospective design to examine the relationship of stress on immunity. Prior to treatment, the mean stress across individuals was 21.10 (SD=9.11). Compared to the general population (Mean=19.62, SD=7.49), the initial measurement of stress in the sample was slightly higher. However, participants' stress levels decreased over time and at 6 months the PSS mean was 17.24 (SD=8.68). This suggests that these patients did not have higher

levels of stress when compared to the general population. One explanation for the reduction of stress over time is that patients gradually adjusted to the diagnosis and treatment. However another explanation may be that the participants with higher levels of stress were nearer to death and either were too ill to complete the assessments or subsequently died; therefore, it appeared that fewer individuals reported high levels of stress at 4- and 6-months follow-up.

Stress levels predicted both percent and absolute numbers of CD16+ and CD56+. The absolute numbers refer to the total number of cells, while the percent CD16+ or CD56+ is relative to the total number of all lymphocyte subsets (taken from complete blood count). These NK cell subsets are critical in the surveillance and destruction of tumor cells. Tauber and Moser have suggested that stress likely affects the NK cells through the HPA axis via an increase and/or decrease in cortisol and possible decrements in IL-1, a cytokine involved in the production of NK cells (Tauber & Moser, 1999). Therefore, high stress levels may decrease the body's defenses to identify and destroy new tumor cells and contribute to the growth of the primary tumor or metastatic spread of the disease.

Cross lagged panel analyses showed that higher stress levels predicted percent CD16+ in the high abnormal range at 4 months before predicting percent CD16+ in the low abnormal range at 6 months. CD16+ is involved in the NK cells response to antibodies (Murphy, Travers, & Walport, 2008); it aids the immune system in recognizing foreign cells and responding to these cells by mounting an attack (antibody-dependent cell-mediated cytotoxicity). The stress induced reduction of this lymphocyte subset might allow abnormal cells in the body to flourish, unchecked by the immune system (Kiecolt-Glaser & Glaser, 1999). This could allow for disease progression in cancer patients and most likely expand the rate of metastasis (Kiecolt-Glaser & Glaser, 1999).

The cross-lagged panel analyses also showed decrements in absolute/percent CD56+ with increased stress. Similar to CD16+, percent CD56+ in the abnormal high range was predicted by stress at

4 months and then percent CD56+ in the abnormal high range at 6 months. The CD56+ lymphocyte is a subset commonly used to identify NK cells (Chan et al., 1997), so the number of lymphocytes available has a direct correlation to CD56+. The reductions of CD56+ caused by stress corresponds to a drop in the absolute levels of NK cells available, so stress-induced depression of CD56+ percentages may mean a reduction of the number of NK cells in the periphery. An overall decline in lymphocytes in the body could result in decreased immunity; not only reduced ability to respond to pathogens but a decreased ability to surveil and combat cancer. It appears that the duration of stress is important, as is evidenced by significant cross-lagged panel findings and cross sectional analyses occurring at 4-month or 6-month follow up.

While acute stress is often transient and has been found to activate the immune system (Goebel, Mills, Irwin, & Ziegler, 2000), chronic stress is known to depress the immune system (Zakowski, Hall, & Baum, 1992). With regard to the cross-lagged panel analyses, this suggests that participants may have been experiencing acute stress at the 4-month follow up but by 6 months a significant link between stress and CD16+ and CD56+ was observed.

Stress level and lymphocyte subset from the prior time point accounted for a significant amount of variance at subsequent time points. The unexplained variance may be explained by comorbid symptoms such as depression, substance use, and sleep disturbances that are often comorbid with stress and immunity (Brady & Sinha, 2007; Irwin, 2008; Muscatell, Slavich, Monroe, & Gotlib, 2009; Sinha, 2008; Thoits, 2010), and other comorbid medical conditions or treatments that may be associated with immune system dsyregulation.

The results of this study are consistent with prior research in that stress was shown to be associated with immune system dysregulation. The rare cases where immune markers predicted stress may be explained by worsening of disease, which could have increased the perceived stress of the

patient. This study also provides support for Andersen's Biobehavioral Model (B. L. Andersen, et al., 1994).

There were several limitations of the study. Attrition due to death was a significant problem; 60% of the participants did not complete the assessment at 6-months (48% of attrition due to death). As the disease advanced, patients were unable to complete interviews or blood work despite doing the interviews by phone and permitting the patient to have blood drawn at a local laboratory. The remaining 12% of patients who did not complete the assessment at 6 months were likely lost to follow-up or were unable to complete the interviews or blood work secondary to advancing disease and placement in hospice care. Furthermore, a small percentage of the patients also were recently recruited and the follow-up not yet completed.

Another limitation might be the PSS used to measure stress. The patients with advanced cancer most likely were experiencing existential stress rather than the stress as defined by the PSS, which reflects stress at different stages of life. An inability of the PSS to measure existential stress would also help explain why the stress observed in this sample is similar to that of the general population. Future direction might look into developing instruments to better assess stress in advanced cancer patients.

The clinical applications of this study are clear – developing interventions that are designed to lower stress in patients with cancer can lead to improvements in immune system functioning even when the cancer presents at advanced stages. Nelson and colleagues provided telephone counseling to patients suffering from cervical cancer as a form of stress management (Nelson et al., 2008). They found that decreases in stress were associated with increases in lymphocyte precursor cells – cells that would eventually mature into NK cells and other immune markers.

Furthermore, Antoni & Lutendorf demonstrated that stress-management interventions can lead to improvements associated with tumor-growth processes. They suggested that stress management facilitates the restoration of disrupted cortisol levels in the body and further noted that this is of great consequence because stress-induced cortisol changes might impair tumor defenses and treatment (Antoni & Lutgendorf, 2007). Also, studies have shown that these psychosocial interventions may lead to a lymphocyte proliferation response in those with cancer (Barbara L. Andersen et al., 2004; McGregor et al., 2004). Furthermore, psychosocial interventions can assist cancer survivors in reducing emotional distress and improving quality of life (Osborn, Demoncada, & Feuerstein, 2006). These improvements in patient quality of life could also lead to better survival rate (Nelson, et al., 2008).

Together these results suggest that psychosocial intervention (more particularly stress management strategies) for patients diagnosed with cancer or other chronic diseases may have immense value because of the benefits of reducing stress and improving immune system functioning. However, previous studies have also shown that interventions may not improve health or quality of life (Bordeleau et al., 2003). Future directions should include testing the biobehavioral model in a larger sample with longer follow-up.

Figure 1. Andersen's Biobehavioral Model (B. L. Andersen, et al., 1994)

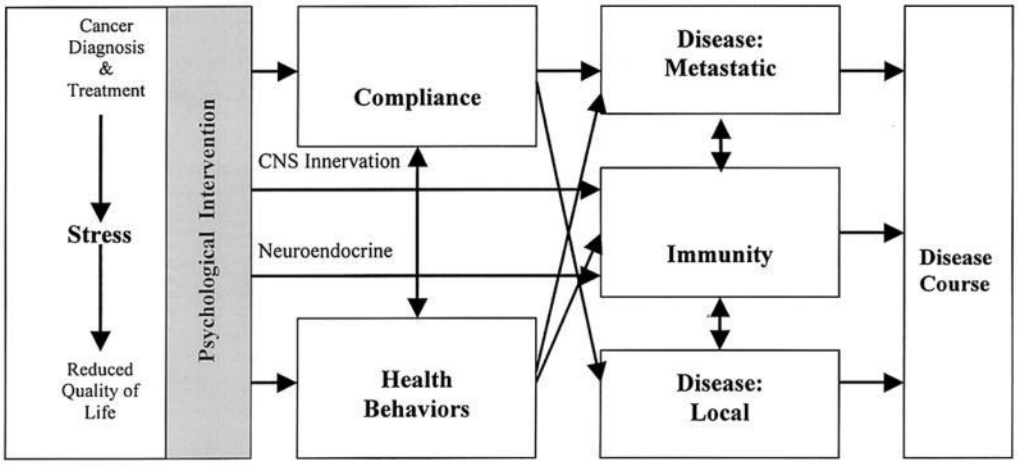

Figure 2. Stress and Percent CD16+ from Baseline to 4-months

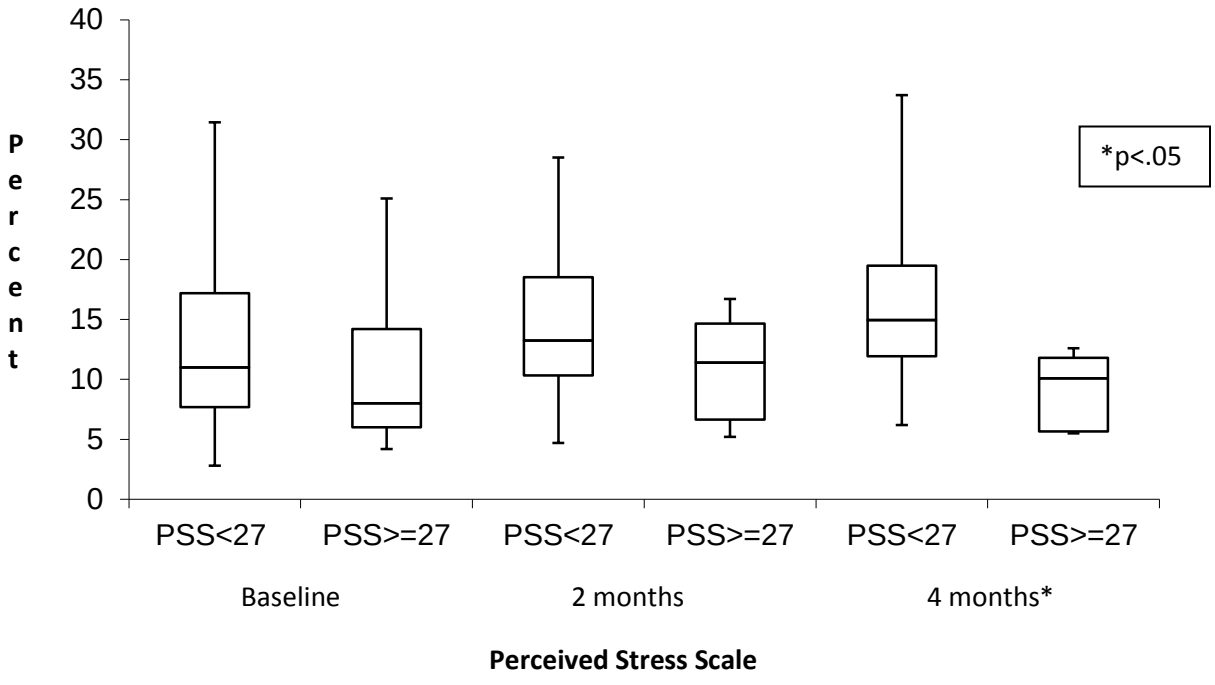

Figure 3. Stress and Percent CD56+ from Baseline to 4-months

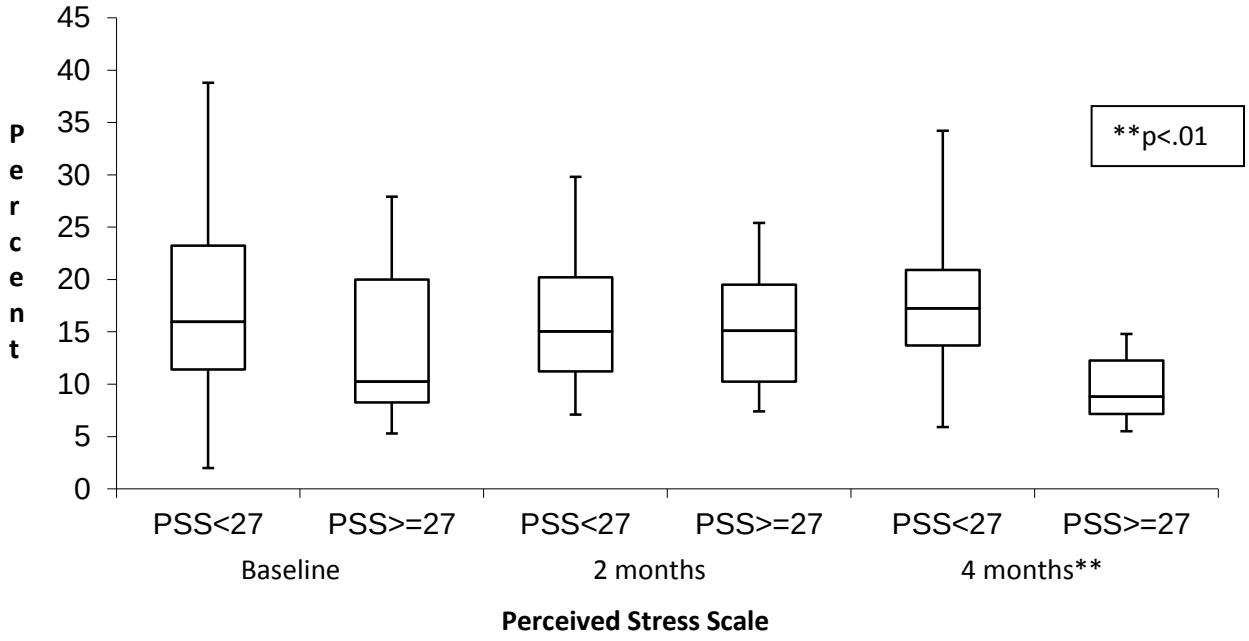

Figure 4. Stress and Absolute Number CD16+ from Baseline to 4-months

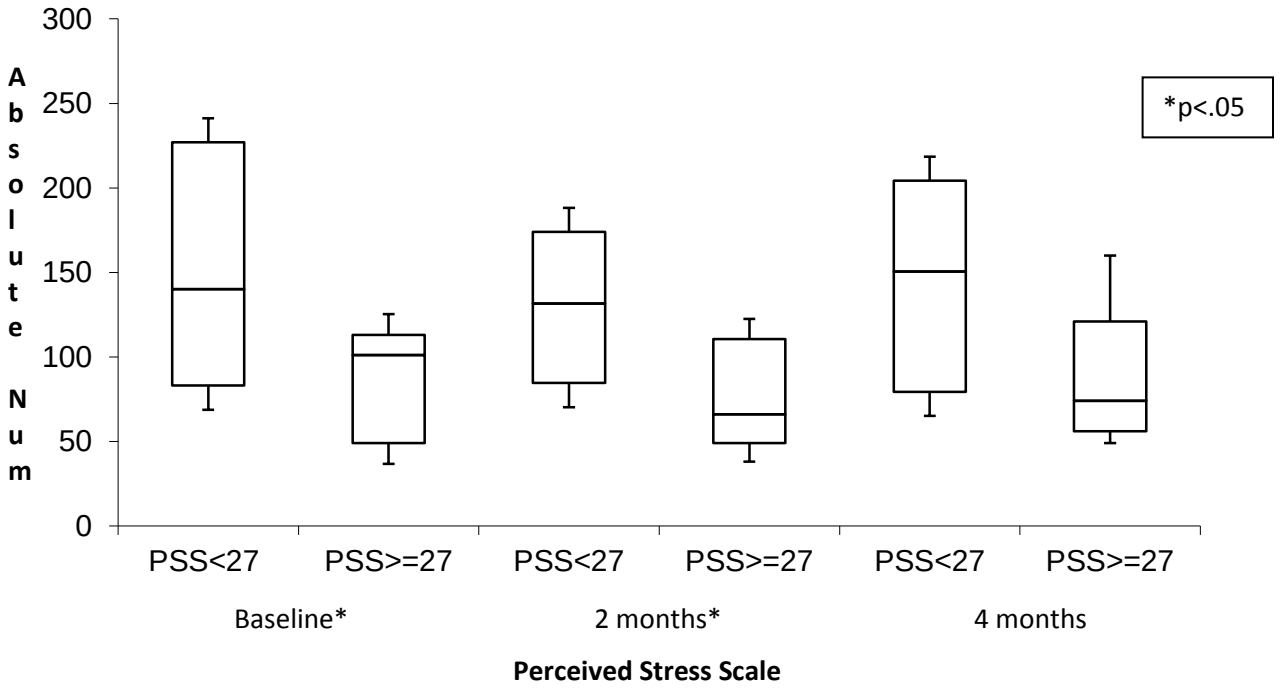

Figure 5. Stress and Absolute Number CD56+ from Baseline to 4-months

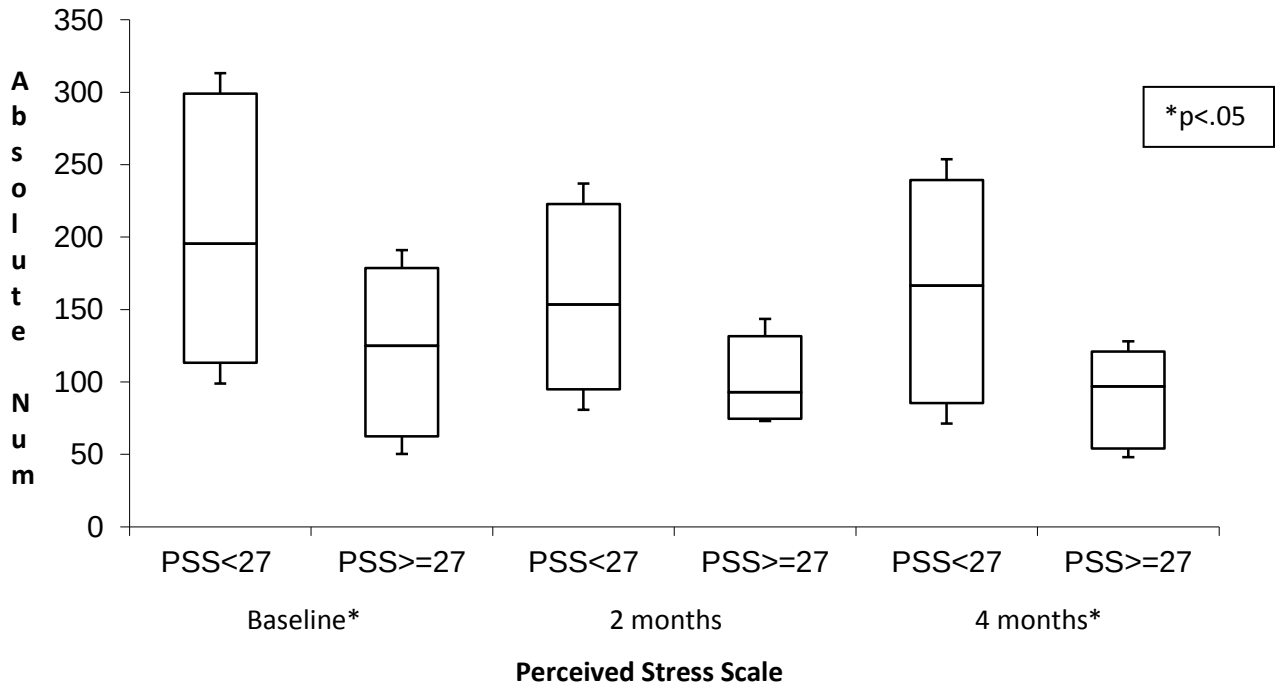

Figure 6. Cross-lagged Panel Analysis CD16+ linking Stress and percent CD16+ from baseline to 6-months

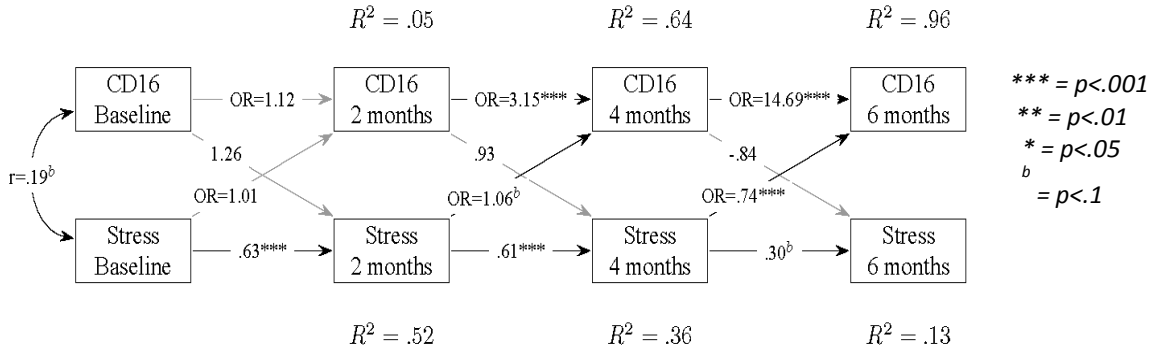

Figure 7. Cross-lagged Panel Analysis CD56+ linking Stress and percent CD56+ from baseline to 6-months

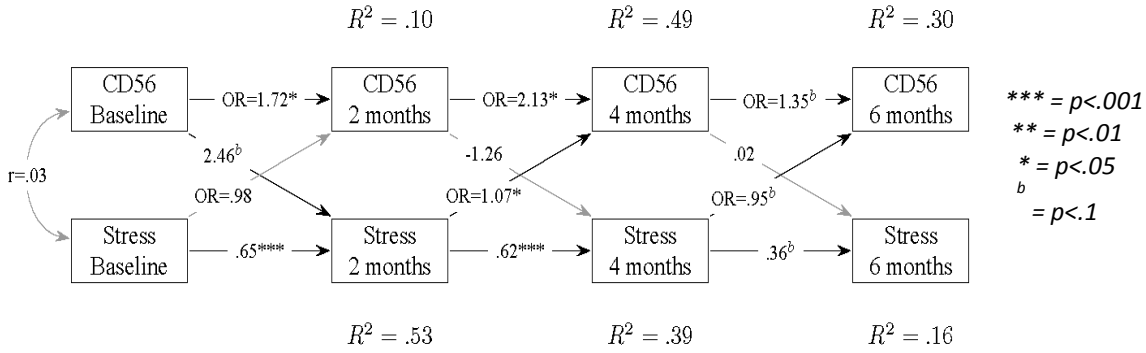

Table 1. PSS Descriptives

Time of Assessment	**PSS** (Mean, SD)
Baseline	21.10, 9.11
2-months	18.87, 8.00
4-months	18.79, 8.47
6-months	17.24, 8.68
Cohen Standardization sample	19.62, 7.49

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