Interleukin-6, Cortisol, and Depressive Symptoms in Ovarian Cancer Patients


ABSTRACT

Purpose
Inflammatory processes have been implicated in the pathogenesis of both depression and cancer. Links between depressive symptoms, interleukin-6 (IL-6), and cortisol dysregulation have been demonstrated in cancer patients, but vegetative versus affective components of depression have been minimally examined. The objective of the current study was to examine associations between IL-6, diurnal cortisol rhythms, and facets of depression in epithelial ovarian cancer patients.

Patients and Methods
Patients awaiting surgery for a pelvic mass suspected for ovarian cancer completed questionnaires, collected salivary samples for 3 days presurgery, and gave a presurgical blood sample. Ascites was obtained during surgery. IL-6 was measured by enzyme-linked immunosorbent assay and cortisol by a chemiluminescence immunoassay. The final sample included 112 invasive ovarian cancer patients (86 advanced stage, 26 early stage) and 25 patients with tumors of low malignant potential (LMP).

Results
Advanced-stage ovarian cancer patients demonstrated elevations in vegetative and affective depressive symptoms, plasma IL-6, and the cortisol area under the curve (AUC) compared with patients with LMP tumors (all P < .05). Among invasive ovarian cancer patients, greater vegetative depression was related to elevated IL-6 in plasma (P = .008) and ascites (P = .024), but affective depression was unrelated to IL-6. Elevations in total depression (P = .028) and vegetative depression (P = .005) were also related to higher evening cortisol levels. Plasma IL-6 was related to greater afternoon and evening cortisol and cortisol AUC (all P values < .005).

Conclusion
These results demonstrate significant relationships between IL-6, cortisol, and depressive symptoms, and may have implications for treatment of depression in ovarian cancer patients.

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INTRODUCTION

Depression is common among cancer patients, approximately one third of whom report depressive symptoms around the time of diagnosis and up to one fourth of whom suffer from major depression. Ovarian cancer patients, who have the poorest survival rate among gynecologic cancer patients, show high rates of depression. Depression among cancer patients has frequently been attributed to the stress of a potentially life-threatening diagnosis and the difficulties of cancer treatment. However, several recent studies among cancer patients have found associations among depression, elevated levels of the proinflammatory cytokine interleukin-6 (IL-6), and/or dysregulation of the neuroendocrine hormone cortisol. Inflammation has been implicated in the pathogenesis of depression as well as cancer, and it has been proposed that tumor-derived inflammatory cytokines such as IL-6 may contribute to depression in cancer patients. However, there has been little systematic investigation of these relationships among cancer patients before potentially confounding treatment with surgery and chemotherapy.

IL-6 is a 21- to 28-kD protein, produced by multiple sources, that serves as a major regulatory cytokine in the human body. It is secreted at high levels by ovarian tumor cells and stimulates key proinflammatory processes in ovarian cancer growth and metastasis including angiogenesis, proliferation, attachment,
In ovarian cancer, elevated IL-6 has been associated with larger tumors, faster tumor progression, decreased chemotherapy effectiveness, poorer clinical status, recurrence, and shorter survival.18-20

In healthy adults, elevated IL-6 has been associated with depressive symptoms21 and clinical depression,22,23 although at least one study with a healthy, nonclinically depressed sample, and a sample of hospitalized patients have failed to show these associations.24,25 IL-6 and other proinflammatory cytokines have profound effects on the CNS, inducing a syndrome of “sickness behaviors” characterized by anhedonia and vegetative symptoms including fatigue, malaise, anorexia, difficulty concentrating, reduced activity, sleep impairments, and disininterest in activities.26,27 Proinflammatory cytokines exert differential effects on affective and vegetative depression, with more prominent effects on vegetative symptoms.27 Affective and vegetative depressive symptoms are thought to occur via distinct mechanisms, with vegetative symptoms occurring significantly earlier than mood disturbance.14,27

Depressive symptoms are also associated with hypercortisol- emia, downregulated glucocorticoid receptors, and general dysregulation of the hypothalamic pituitary adrenal (HPA) axis.28 With chronic stress and depression, the negative feedback system regulating cortisol may become impaired29 and diurnal cortisol rhythms altered, particularly with respect to evening cortisol.30-33 There is a well-characterized feedback loop whereby IL-6 stimulates HPA secretion of cortisol which exerts negative feedback on IL-6 for inflammatory control.32,33 Persistent infiltration is associated with HPA abnormalities and may contribute to the hypercortisolism seen in depression.14,28 Cancer patients often demonstrate restricted and dysregulated cortisol rhythms.8,9,34

There has been minimal examination of components of depression (eg, affective vs vegetative) that most strongly relate to IL-6 and cortisol abnormalities in cancer (described in Appendix, online only). The objectives of the current study were to contrast levels of IL-6, cortisol, and depressive symptoms according to severity of ovarian cancer, and to examine associations among IL-6, diurnal cortisol rhythms, and components of depression to shed light on unique mechanisms contributing to affective and vegetative depressive symptoms. Participants included two groups of ovarian cancer patients with invasive disease: early stage (I and II) and advanced stage (III and IV). Patients with ovarian tumors of low malignant potential (LMP) served as the comparison group. 25 patients with LMP tumors.

**Psychosocial Measures**
The Center for Epidemiological Studies-Depression Scale (CES-D) is a validated 20-item measure on which subjects rate frequency of depressive symptoms over the previous week on a four-point scale ranging from 0 (rarely)
to 3 (most or all of the time). Scores of 16 or higher have been associated with clinical depression. A four-factor structure has been identified for the CES-D with the following subscales: depressed affect, positive affect, vegetative symptoms, and interpersonal relations. These factors have been used independently to provide a more accurate picture of facets of depression, particularly for individuals with chronic illness. Patients also completed information about demographic characteristics and health behaviors such as sleep, caffeine, and smoking.

**Statistical Analyses**

Distributions were examined for outliers and non-normality. IL-6 data were normalized by logarithmic transformation. Cortisol data were examined...
for sampling time outliers and then for cortisol value outliers. Acceptable sampling times were determined to fit the maximum number of participants, while retaining homogeneity. First morning cortisol values were excluded if they were outside the window of 4 to 9 AM. Afternoon values from 3 to 6 PM and evening values from 8 PM to midnight were included in analyses. Cortisol values more than four standard deviations from the mean for any time point were classified as outliers and replaced with the highest acceptable value as performed previously. Mean cortisol values for each patient at each time point were calculated over the 3 collection days. Data were then normalized using natural log transformations. Area under the curve (AUC) over 24 hours was calculated using the trapezoidal formula.

Between-group differences for continuous variables were tested by one-way analyses of variance (ANOVAs) and differences in categoric variables were tested using $\chi^2$ analyses. Univariate analyses of covariance (ANCOVAs) adjusting for age were performed to test whether depression, IL-6, and cortisol (AUC) levels differed between the three groups. Post hoc tests comparing each pair of groups were conducted after significant ANCOVA models used two-sided tests of significance with Bonferroni-adjusted $P$ values. An adjusted $P$ value of less than .05 was considered significant. Because only two patients with LMP tumors and five early-stage patients had ascites, between-group analyses for ascites IL-6 were not conducted. Linear mixed-models adjusting for age examined whether change in cortisol over time varied by group. ANCOVAs then examined between-group differences at each time point. Multiple regression models adjusting for age and stage were conducted to examine relationships between depression, IL-6, and cortisol among invasive ovarian cancer patients.

**RESULTS**

Demographic Information

Demographic and clinical characteristics are shown in Table 1. Patients with LMP tumors were significantly younger than patients with advanced-stage disease [$F(1,134) = 8.87, P = .009$]; therefore, age was included as a covariate in between-group analyses. There were no significant differences among the three groups with regard to smoking status, use of alcohol, caffeine, hours of sleep over the previous night or week, exercise frequency, income, or education (all $P > .12$). Among invasive ovarian cancer patients, stage was associated with plasma IL-6 ($r = .23, P = .025$), age and stage were significantly associated with cortisol levels for at least one cortisol time point ($P < .05$), and caffeine was associated with lower

![Fig 1.](image-url) Age-adjusted means (and SE bars) for Center for Epidemiologic Studies-Depression Scale (CES-D) among advanced- and early-stage invasive ovarian cancer patients and patients with tumors of low malignant potential (LMP). (A) CES-D total, (B) positive mood subscale, (C) vegetative depression subscale, (D) depressive mood subscale, and (E) depressive interaction subscale. All significance levels are Bonferroni adjusted.
afternoon cortisol ($r = -0.033, P = 0.033$). Age and stage were therefore used as covariates for all regression analyses; analyses with afternoon cortisol adjusted for caffeine. No other potential covariate was significantly associated with IL-6 or cortisol values ($P > 0.06$).

**Depressive Symptoms**

Patients with advanced-stage disease reported significantly greater total depressive symptoms (CES-D total) than patients with LMP tumors ($F(1,133) = 15.02, P = 0.005$; omnibus tests are show in Appendix Table A1, online only). Early-stage patients did not differ significantly in total depression from the other two groups, ($P > 0.08$; Fig 1A). Significantly more advanced-stage patients (57%) than patients with LMP tumors (28%) had CES-D scores in the range of clinical depression [$\chi^2(111) = 6.51, P = 0.011$]. Early-stage patients did not significantly differ from the other two groups in the proportion of clinically depressed patients (38%; $P > 0.09$). Advanced-stage patients reported significantly less positive mood than patients with early-stage disease [$F(1,133) = 6.91, P = 0.029$], or LMP tumors [$F(1,133) = 13.92, P = 0.008$], who did not differ from each other ($P = 0.92$). Advanced-stage patients reported significantly greater vegetative depression [$F(1,133) = 9.49, P = 0.008$] and depressed mood [$F(1,133) = 6.08, P = 0.045$] but no difference in interpersonal difficulties [$F(1,133) = 5.26, P = 0.07$] compared with patients with LMP tumors. Early-stage patients did not differ significantly in these facets of depression from the other two groups ($P > 0.15$; Figs 1B-1E).

**IL-6**

Plasma IL-6 levels among advanced-stage patients ($M = 14.72 \pm 8.36$ pg/mL) were substantially elevated above a cutoff (3.19 pg/mL) previously associated with greater all-cause mortality in community-dwelling elders, and were significantly higher than those of patients with LMP tumors [$F(1,111) = 23.79, P < 0.0001$]. IL-6 levels of early-stage patients were between levels of the two other groups [early $\chi^2$ advanced stage, $F(1,111) = 5.67, P = 0.057$; early stage $\chi^2$ LMP, $F(1,111) = 4.85, P = 0.09$; Fig 2A]. Mean ascites IL-6 was profoundly elevated in both groups of invasive cancer patients who did not differ significantly from each other ($P = 0.81$; Table 2).

**Cortisol**

Salivary cortisol levels in all patients were elevated above population norms at each assessment, with evening levels in invasive patients approximately three times healthy population norms. The cortisol AUC was significantly higher among advanced-stage patients than among patients with LMP tumors [$F(1,153) = 6.24, P = 0.047$] but early-stage patients did not differ from the other two groups ($P > 0.50$; Fig 2B). Diurnal cortisol levels did not differ significantly among the three groups at any time point ($P > 0.06$) or over the day ($P > 0.73$; Table 2).

**Depressive Symptoms, IL-6, and Cortisol Among Invasive Ovarian Patients**

Multiple regression analyses examined relationships between IL-6 and facets of depression in early- and advanced-stage patients. Because their regression slopes did not differ significantly, both groups of invasive ovarian cancer patients were combined in analyses, adjusting for age and stage. Invasive ovarian cancer patients with greater vegetative depression had higher IL-6 in both plasma ($\beta = 0.27, P = 0.008$, effect size [ES] = 0.07) and ascites ($\beta = 0.31, P = 0.024$, ES = 0.93; Figs 3A and 3B). Elevations in total depression ($\beta = 0.33, P = 0.026$, ES = 0.10) and vegetative depression ($\beta = 0.43, P = 0.005$, ES = 0.17) were related to higher evening cortisol, and vegetative depression was also related to higher afternoon cortisol ($\beta = 0.29, P = 0.04$, ES = 0.08). Other facets of depression and total depression were not significantly related to IL-6 or cortisol at any time point, or to the cortisol AUC ($P > 0.15$).

Plasma IL-6 was related to greater evening cortisol ($\beta = 0.48$, $P < 0.0003$, ES = 0.21), afternoon cortisol ($\beta = 0.58, P < 0.0001$, ES = 0.25), and cortisol AUC ($\beta = 0.49, P = 0.003$, ES = 0.22). Ascites IL-6 was marginally associated with greater evening cortisol ($\beta = 0.45, P = 0.056$, ES = 0.17) but not to other cortisol values.

This study extends previous work by documenting elevations of IL-6 and both affective and vegetative depressive symptoms in advanced-stage ovarian cancer patients presurgery. Early-stage patients generally had levels of IL-6 and depressive symptoms that were greater than those observed in LMP patients but lower than those in patients with advanced disease. Among patients with invasive disease, only the
The excessive production of IL-6 by ovarian carcinomas may set up a chronic proinflammatory state, eliciting sickness behaviors and contributing to depressive symptomatology via cytokine regulation of CNS function.14

Several possible mechanisms may contribute to depression in invasive ovarian cancer patients, all of which may operate simultaneously. Because patients with more advanced cancers demonstrated the greatest vegetative symptoms, it is possible that physical symptoms secondary to the bulk of the tumor, including bowel difficulties and distention, may contribute to vegetative symptoms. Additionally, although assessments of depressive symptoms were made before patients knew their diagnosis and prognosis, ovarian cancer has been associated with elevated depression,46 and concerns about ovarian cancer may have contributed to elevated depressive symptoms.

It is also possible that elevated levels of tumor-derived IL-6 directly contribute to the development of “sickness behaviors” that overlap with symptoms of vegetative depression,26 although the extent of independent effects by IL-6 relative to other cytokines is not clear.49 Proinflammatory cytokines influence the CNS via several direct pathways, including passage through regions of permeability of the blood-brain barrier and stimulation of afferent fibers in the vagus nerve. These fibers relay information to specific brain nuclei with subsequent downstream effects on multiple central processes including induction of cytokines, neurotransmitters, stimulation of the HPA axis, and development of sickness behaviors.26-28,50 Relationships between IL-6 and vegetative depression accompanied by the absence of associations between affective depression and IL-6 are consistent with the possibility that inflammatory mechanisms may contribute to vegetative symptoms,27 whereas other mechanisms may underlie affective symptoms of depression.

There are also well-established links between the HPA axis and depression.12,27,51 Chronic inflammation can induce glucocorticoid resistance52,53 and lead to a hyperactive HPA axis along with suppressed negative feedback.27 The resultant HPA dysregulation and high levels of cortisol may contribute to depression,50 providing an indirect pathway between IL-6 and depression.

Table 2. Age-Adjusted Means of Psychosocial and Physiological Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>No. of Patients</th>
<th>Patients With LMP Tumors</th>
<th>Early-Stage Ovarian Cancer Patients</th>
<th>Advanced-Stage Ovarian Cancer Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LMP Early Advanced Mean 95% CI</td>
<td>Mean 95% CI</td>
<td>Mean 95% CI</td>
<td>Mean 95% CI</td>
</tr>
<tr>
<td>CES-D</td>
<td>Total score</td>
<td>25 26 86</td>
<td>10.40 6.92 to 13.88</td>
<td>13.96 10.61 to 17.31</td>
</tr>
<tr>
<td></td>
<td>Vegetative</td>
<td>25 26 86</td>
<td>4.90 3.28 to 6.54</td>
<td>6.05 4.48 to 7.62</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>25 26 86</td>
<td>9.27 8.11 to 10.44</td>
<td>8.46 7.34 to 9.58</td>
</tr>
<tr>
<td></td>
<td>Depressed mood</td>
<td>25 26 86</td>
<td>1.86 0.58 to 3.13</td>
<td>3.46 2.23 to 4.69</td>
</tr>
<tr>
<td></td>
<td>Interpersonal</td>
<td>25 26 86</td>
<td>0.92 0.42 to 1.42</td>
<td>1.14 0.66 to 1.62</td>
</tr>
<tr>
<td>IL-6 pg/mL</td>
<td>Plasma</td>
<td>20 23 72</td>
<td>4.07 2.57 to 6.31</td>
<td>8.13 5.25 to 12.45</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
<td>2 5 50</td>
<td>1169.49 246.60 to 5564.26</td>
<td>3854.78 1442.11 to 10303.86</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>AM</td>
<td>18 12 36</td>
<td>14.15 10.39 to 19.11</td>
<td>17.64 12.00 to 24.58</td>
</tr>
<tr>
<td></td>
<td>AM +30</td>
<td>17 13 34</td>
<td>19.53 15.41 to 24.78</td>
<td>21.63 16.49 to 28.36</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>18 13 32</td>
<td>6.30 5.03 to 7.89</td>
<td>6.69 5.11 to 8.77</td>
</tr>
<tr>
<td></td>
<td>Night</td>
<td>19 14 34</td>
<td>4.91 3.39 to 7.09</td>
<td>7.24 4.71 to 11.09</td>
</tr>
<tr>
<td></td>
<td>AUC</td>
<td>17 10 30</td>
<td>51.06 45.98 to 56.12</td>
<td>54.28 47.52 to 61.03</td>
</tr>
</tbody>
</table>

Abbreviations: LMP, low malignant potential; CES-D, Center for Epidemiological Studies-Depression Scale; AUC, area under the curve; ES, effect size.

*Significantly different from LMP at P ≤ .001, ES = .10.
†Significantly different from LMP at P < .01, ES = 0.067.
‡Significantly different from early stage at P < .05, ES = 0.05.
§Significantly different from LMP at P < .05, ES = 0.04.
¶Significantly different from LMP at P ≤ .001, ES = 0.18.
††Significantly different from LMP at P < .05, ES = 0.11. All significance levels are Bonferroni adjusted.

vegetative component of depression was linked with IL-6 and evening cortisol. Aspects of depression related to affect were not associated with either IL-6 or cortisol, suggesting that different mechanisms may underlie affective versus vegetative depression in these patients. Elevated IL-6 was also related to greater disturbances in the diurnal cortisol rhythm among invasive ovarian cancer patients, with elevated plasma and ascites IL-6 related to higher evening cortisol, and plasma IL-6 also related to higher afternoon cortisol and cortisol AUC. IL-6 means among advanced-stage patients were greater than a cutoff of 10.9 pg/mL, previously associated with depression in metastatic cancer patients.9 The present results are consistent with the “proinflammatory cytokine theory of depression” in suggesting that pathophysiologic elevations in circulating inflammatory mediators may drive the appearance of depressive symptomatology via cytokine regulation of CNS function.14

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setting up a positive feedback loop for IL-6 in the tumor microenvironment. It is also possible that all of these pathways may operate simultaneously.

These findings are correlational and thus limit causal inferences. We are currently using an experimental animal model of ovarian cancer to further understand these issues. To accommodate surgical scheduling and limit circadian variability of IL-6, blood sampling was performed between 6 AM and noon. IL-6 was not related to blood sampling time, suggesting minimal circadian contribution to variability. Some patients were missing one of the physiological variables, particularly cortisol values; this may have contributed to loss of power, and these findings should be interpreted with caution.

Our findings provide a new understanding of relationships between an important proinflammatory cytokine (IL-6), cortisol, and depressive symptoms in ovarian cancer. Moreover, these results raise intriguing questions regarding whether tumor IL-6 production contributes to vegetative depression in ovarian cancer. Further mechanistic work is needed to clarify such questions and may offer hope for novel pharmacologic treatments for vegetative depression in ovarian cancer.61

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Susan K. Lutgendorf, Anil K. Sood, David M. Lubaroff

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Administrative support: Susan K. Lutgendorf, Frank Penedo, David M. Lubaroff

Provision of study materials or patients: Susan K. Lutgendorf, Frank Penedo, Koen DeGeest, Joseph A. Lucci

Collection and assembly of data: Susan K. Lutgendorf, Aliza Z. Weinrib, Frank Penedo, Patrick J. Henderson, David M. Lubaroff


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Appendix

Depression is a multifaceted construct including components such as neurovegetative and somatic symptoms as well as psychological symptoms that include mood and cognitive alterations. Low positive and high negative affect are thought to be independent components of depression, resulting from different biobehavioral mechanisms (Watson D, Wiese D, Vaidya J, et al. J Personality Social Psychol 76:820-838, 1999). The Center for Epidemiological Studies Depression scale has a stable four-factor measurement structure that identifies four dimensions of depressive symptoms: positive mood, negative mood, vegetative symptoms, and interpersonal symptoms (such as feeling like a failure, etc; Sheehan TJ, Fifield J, Reisine S, et al. J Personality Assess 64:507-521, 1995). In depression induced by inflammatory cytokines, neurovegetative and somatic symptoms such as fatigue, anorexia, pain, reduction in movement, and sleep disorders predominate, and tend to have an early onset. Psychological symptoms of depression occur later (Capuron L, Gumnick JF, Musselman DL, et al. Neuropsychopharmacology 26:643-652, 2002; Capuron L, Dantzer R. Brain Behav Immun 7:S119-S124, 2001; Capuron L, Ravaud A, Dantzer R. J Clin Oncol 18:2143-2151, 2001; Dantzer R, O’Connor JC, Freund GG, et al. Nat Rev Neurosci 9:46-57, 2008). We have previously reported that the vegetative symptom of fatigue was related to elevated IL-6 in plasma and ascites in advanced-stage presurgical ovarian cancer patients, and that patients with a self-reported history of depression had higher presurgical IL-6 (Costanzo ES, Lutgendorf SK, Sood AK. Cancer 104:305-313, 2005). Understanding which components of depression are related to an inflammatory cytokine such as IL-6 sheds light on potential etiology of symptoms. Thus, if IL-6 is related to vegetative depression but not to affective depression, this would be consistent with an interpretation that this inflammatory cytokine may contribute to the symptoms of vegetative depression, whereas another mechanism may underlie the affective component of depression. Because in ovarian cancer IL-6 is largely tumor derived (Burger RA, Grosen EA, Ioli GR, et al. Spontaneous release of interleukin-6 by primary cultures of lymphoid and tumor cell populations purified from human ovarian carcinoma. J Interferon Cytokine Res 5:255-260, 1995), the implication of this finding is that a tumor-derived product is driving the depression.

Table A1. Summary of Between-Group Analyses

<table>
<thead>
<tr>
<th>Measure</th>
<th>Omnibus ANOVA df</th>
<th>Post hoc Tests df</th>
<th>LMP v Early-Stage Patients df</th>
<th>LMP v Advanced-Stage Patients df</th>
<th>Early-Stage v Advanced-Stage Patients df</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
<td>F</td>
<td>P</td>
<td>F</td>
</tr>
<tr>
<td>CES-D Total score</td>
<td>2,133</td>
<td>8.31</td>
<td>&lt;.0001</td>
<td>1,133</td>
<td>2.15</td>
</tr>
<tr>
<td>Vegetative</td>
<td>2,133</td>
<td>5.48</td>
<td>.005</td>
<td>1,133</td>
<td>1.01</td>
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<tr>
<td>Positive</td>
<td>2,133</td>
<td>8.48</td>
<td>&lt;.0001</td>
<td>1,133</td>
<td>1.00</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>2,133</td>
<td>3.09</td>
<td>.049</td>
<td>1,133</td>
<td>3.23</td>
</tr>
<tr>
<td>IL-6 pg/mL (plasma)</td>
<td>2,111</td>
<td>12.62</td>
<td>&lt;.0001</td>
<td>1,111</td>
<td>4.85</td>
</tr>
<tr>
<td>Cortisol, nmol/L AM</td>
<td>2.62</td>
<td>1.69</td>
<td>.19</td>
<td>1.62</td>
<td>0.81</td>
</tr>
<tr>
<td>Cortisol, nmol/L AM + 30</td>
<td>2.60</td>
<td>2.36</td>
<td>.10</td>
<td>1.60</td>
<td>0.32</td>
</tr>
<tr>
<td>Cortisol, nmol/L PM</td>
<td>2.59</td>
<td>1.71</td>
<td>.19</td>
<td>1.59</td>
<td>0.13</td>
</tr>
<tr>
<td>Night</td>
<td>2.63</td>
<td>1.05</td>
<td>.36</td>
<td>1.63</td>
<td>1.93</td>
</tr>
<tr>
<td>AUC</td>
<td>2.53</td>
<td>3.18</td>
<td>.05</td>
<td>1.53</td>
<td>0.60</td>
</tr>
</tbody>
</table>

NOTE. P values of post hoc tests are Bonferroni corrected. A P value of .99 is given if the Bonferroni adjustment would have made it greater than 1.00. Abbreviations: ANOVA, analysis of variance; LMP, low malignant potential; CES-D, Center for Epidemiological Studies Depression Scale; IL-6, interleukin-6; AUC, area under the curve.