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Letter to the Editor

Lymphopenia and neutrophilia in SARS are related to the prevailing serum cortisol

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Sir,

Unexplained lymphopenia and neutrophilia occurred in patients with Severe Acute Respiratory Syndrome (SARS) [1,2]. Although the coronavirus, implicated in SARS, may have directly caused the aforementioned; glucocorticoids can cause lymphopenia by causing the migration of lymphocytes from the peripheral circulation [3–5], and neutrophilia [3,6] by inhibiting apoptosis [6]. Moreover, glucocorticoids are used in lymphoproliferative diseases as cytolethal agents [7]. Glucocorticoids were used in treating SARS patients, and thus lymphopenia and neutrophilia may have been drug induced. In one study [2], the prevalence of lymphopenia was 54% at admission, but only 40% of the patients were treated with steroids for the first 48 h. Therefore not all of the lymphopenia (and neutrophilia) can be ascribed to exogenous steroids.

Any critical illness including SARS should provoke a stress response, and cause the normal adrenals to secrete 225–440 mg day^{-1} of cortisol [8], an amount that could easily cause T lymphocytes to migrate out of the peripheral circulation. We therefore questioned whether lymphopenia in SARS is reflecting the integrity of the hypothalamic-pituitary-adrenal (HPA) axis, and that patients without lymphopenia are perhaps adrenal insufficient [9]. In this retrospective study, we have examined the relationship between serum cortisol and white blood corpuscles (WBC) in a cohort of SARS patients with or without lymphopenia and neutrophilia.

Sixty-four patients were admitted to the Prince of Wales Hospital in Hong Kong between March and May 2003 and met modified WHO criteria for SARS. This included fever with body temperature of 38 °C or higher, cough or shortness of breath, new pulmonary infiltrates on chest radiograph, and either an exposure to a confirmed SARS' patient or a lack of response to empirical antimicrobial therapy for typical and atypical pneumonia including beta-lactams, macrolides, fluoroquinolones, or tetracyclines. Severe Acute Respiratory Syndrome was subsequently confirmed in all patients by seropositivity and/or positive reverse transcriptase polymerase chain test for SARS-associated coronavirus. Serum specimens from 57 patients, all collected in the morning and before the commencement of therapy, were assayed for cortisol by the electrochemiluminescence immunoassay (Roche Diagnostics Corporation, IN). The intra- and interassay coefficients of variation were 2·0 and 3·0%, respectively. In two patients cortisol exceeded 7220 nmol L^{-1} (peak stress response [8]) and were eliminated before statistical analyses. An aliquot of blood specimen was used for WBC measurements. T lymphocytes ($CD3^+$), B lymphocytes ($CD19^+$), helper T lymphocytes ($CD3^+CD4^+$), suppressor T lymphocytes ($CD3^+CD8^+$), and natural killer lymphocytes ($CD3^-CD16^+$ and/or $CD56^+$) in whole blood were measured by MutliTEST™ IMK Kit along with TruCOUNT Tubes (Becton Dickinson, San Diego, CA) using a 4-colour FACSCalibur flow cytometer (Becton Dickinson). The method had 10% imprecision. Lymphopenia was defined as lymphocyte count < 19% [normal range (NR) 19–47%] and neutrophilia as neutrophil count > 73% (NR 41–73%) of the total WBC. The frequencies of lymphopenia or neutrophilia relative to cortisol deficient (< 414 nmol L^{-1} [10]) or replete state were tested by 2×2 χ^2 test. All data were analyzed using the Statistica software (StatSoft, Tulsa, OK).

We found that serum cortisol correlated positively with neutrophils, and negatively with monocytes and lymphocytes. With lymphocyte subsets, cortisol correlated negatively with suppressor $CD8^+$ cells, B lymphocytes and helper $CD4^+$ cells (all correlations were significant with $P < 0{\cdot}05$, see Table 1). In 54 out of 59 patients lymphopenia concurred with neutrophilia, but lymphocytes were not inversely correlated with neutrophils. Cortisol was significantly higher in the lymphopenic compared with

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Table 1 Correlation of blood cortisol with total white blood corpuscle and its various cellular components

	WBC and differentials (n = 49)				Lymphocyte subsets (n = 34)				
	WBC	Neutros	Lymphos	Monos	$CD3^+$	$CD4^+$	$CD8^+$	NK	B
Cortisol	0·22	0·31*	−0·36*	−0·30*	−0·43*	−0·35*	−0·56*	−0·05	−0·46*

*Correlations coefficients are significant at $P < 0·05$.
Neutros, neutrophils; Lymphos, lymphocytes; Monos, monocytes; NK, natural killer cells.

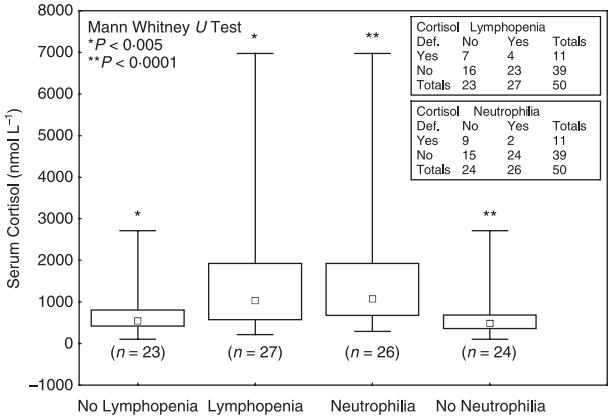

Figure 1 Serum cortisol in Severe Acute Respiratory Syndrome patients with or without lymphopenia or neutrophilia. The little squares represent the median, the large rectangles represent the 25–75th percentile range and the error bars represent the maximum to minimum range. The Mann–Whitney *U*-test comparisons between different groups are depicted by asterisks. The insets show 2×2 frequency tables of cortisol deficiency (def.) (yes or no) against lymphopenia (Pearson χ^2, $P = 0·184$) or neutrophilia (Pearson χ^2, $P = 0·011$) status (yes or no).

nonlymphopenic patients ($P < 0·005$; Mann–Whitney *U*-test) and the neutrophilic compared with non-neutrophilic patients ($P < 0·0001$; Mann–Whitney *U*-test) (Figure 1). The frequency of neutrophilia (24/50; Pearson χ^2, $P = 0·011$) and lymphopenia (23/50; Pearson χ^2, $P = 0·184$) were confined to cortisol replete state (see Figure 1 inset).

This study has shown (i) significant correlations between serum cortisol and numbers of lymphocytes and neutrophils and (ii) that SARS patients with lymphopenia and neutrophilia had significantly higher cortisol than those without. A critical illness such as SARS should cause secretion of 225–440 mg day^{-1} of cortisol with a blood concentration of 883–7220 nmol L^{-1} [8]. The patients exhibiting lymphopenia and neutrophilia had cortisol in this range, which may explain their WBC status. O'Donnell *et al.* suggested that apoptosis may explain lymphopenia in SARS [11], based on their findings of lymphopenia and neutrophilia in children with severe respiratory syncytial virus disease. It is difficult to explain why viral infection causes apoptosis in lymphocytes, but not in neutrophils. As stated earlier, cortisol action can explain both lymphopenia and neutrophilia.

Short-duration high-dose glucocorticoid therapy is ineffective in acute respiratory distress syndrome [8], and steroid usage in SARS has been questioned [12]. Admittedly, the outbreak of SARS caught the medical community totally unprepared in Hong Kong, with the inadvertent use of Ribavarin and steroid therapy to alleviate patients' suffering. It is difficult to say if the patients with lymphopenia and neutrophilia fared any better than those without and vice versa, but it is noteworthy that patients admitted to Intensive Care Units or who eventually died had a significantly higher neutrophil count [1]. Whether the neutrophilia in this group of patients was a reflection of steroid treatment remains unanswered.

In retrospect, it might be judicious to keep an eye on a patient's HPA axis. The need for steroids should never arise if the HPA axis is functioning normally, and if steroids are at all required they should be reserved for patients with adrenal insufficiency. This, from our study, may be reflected by the lymphopenia and neutrophilia.

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