Research paper

# Contribution of endocrine parameters in predicting outcome of multiple trauma patients in an intensive care unit

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**ABSTRACT**

**OBJECTIVE: To evaluate whether tentative prognostic models for intensive care unit survival of multiple trauma patients could be improved by including endocrine parameters. DESIGN: Prospective study. Patients: Eighty-three male and 11 female multiple trauma patients. Measurements: Upon admission, severity of trauma was assessed with the Acute Physiology and Chronic Health Evaluation II (APACHE II), the Sequential Organ Failure Assessment (SOFA) score and the Injury Severity Score (ISS). Concurrently, blood was drawn to measure thyrotropin (TSH), free thyroxine (fT4), trioodothyronine (T3), corticotropin (ACTH), prolactin (PRL), cortisol and dehydroepiandrosterone sulphate (DHEAS). Adrenal reserve was assessed with the Synacthen test. RESULTS: Seventy-five of the 83 men and 8 of the 11 women survived. APACHE II and SOFA scores were higher in non-survivors compared to survivors (with considerable overlap). From the baseline endocrine work-up, survivors had higher ACTH and DHEAS values compared to non-survivors (also with considerable overlap). No differences between survivors and non-survivors were noted in the Synacthen test or in thyroid function tests. Nevertheless, a multivariate logistic regression model that incorporated the APACHE II score and hormonal parameters (Cortisol post-Synacthen, DHEAS, TSH*age) was well-fitted to assess survival/non-survival as an endpoint and better than APACHE II, SOFA or ISS scores alone to predict ICU survival or death. CONCLUSION: In critically ill multiple trauma patients, age, TSH, Cortisol post-Synacthen and DHEAS values upon admission to the ICU, combined with the APACHE II score, may predict outcome more accurately than the APACHE II score alone.**

**Key words:** Adrenal, Anterior pituitary hormones, Endocrine parameters, Intensive care unit, Logistic Models, Multiple trauma, ROC Curves, Thyroid

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## INTRODUCTION

The endocrine milieu of patients hospitalized in intensive care units (ICU) and/or in critical condition has been assessed in many studies[1] and differences in pituitary, thyroid and adrenal function have been found between survivors and non-survivors.[2] Nevertheless, an overlap of hormone values between patients in critical condition compared to controls or ICU survivors and non-survivors is generally noted in relevant studies. In a recent study of 206 patients, a logistic regression model incorporating a well-established clinical measure of ICU patients evaluation (the Acute Physiology and Chronic Health Evaluation II; APACHE II score), free triiodothyronine (fT3) and thyrotropin (TSH) values was shown to add to the prognostic value of APACHE II in patients with acute respiratory distress syndrome (ARDS).[3] In the aforementioned study no patients with trauma were included. In another recent study of 113 ICU patients (with only 4 of them admitted because of trauma), the addition of TSH and total T3 improved the prognostic value of the APACHE II score.[4] An older study of 260 ICU patients (with only 5 of them admitted because of trauma) showed that the combination of TSH, thyroxine (T4) and cortisol was a better predictor of survival than the APACHE II score.[2] Interestingly, TSH values in earlier studies of fewer ICU patients with trauma were mostly low[5] or suppressed[6] but were not associated with survival.[7,8] Among other endocrine parameters, "occult" or frank adrenal insufficiency[9] has been linked in some studies with an adverse outcome of patients with trauma,[10] but not in others.[11,12] The aim of the present study was to evaluate whether or not prediction of outcome in ICU patients with trauma could be improved by combining clinical assessment models with parameters of pituitary, thyroid and adrenal function.

## SUBJECTS AND METHODS

### *Subjects*

This was a prospective study of 83 male and 11 female (age [mean±sd] 35.8±16.6 years) trauma patients (63 with head trauma) hospitalized at a single tertiary-care teaching hospital's ICU from August 2003 to December 2005. Gender was taken into consideration as an independent dichotomous variable in statistical analysis. Exclusion criteria included prior (within the past year) use of corticosteroids, concurrent treatment with drugs affecting the hypothalamic-pituitary activity (etomidate, diphenylhydantoin or rifampicin) and a known pre-existing endocrine disorder. The hospital's ethics committee gave their approval for the performance of the study. Informed consent was obtained from the patients' next of kin.

### *Treatment*

The administration of dopamine (shown to inhibit pituitary hormone secretion and in particular prolactin (PRL)[13,14] or TSH in most,[15-17] but not all,[18] clinical studies) to patients was recorded and was taken into consideration as an independent dichotomous variable in statistical analysis.

### *Measures*

Upon admission in the ICU, severity of trauma was assessed by means of APACHE II, Sequential Organ Failure Assessment (SOFA) score and Injury Severity Score (ISS). Concurrently, blood was drawn to measure TSH, free T4 (fT4), T3, corticotropin (ACTH), PRL, cortisol and dehydroepiandrosterone sulphate (DHEAS). Furthermore, to assess adrenal reserve, cortisol was measured 30 minutes after the intravenous administration of 1 microgram of synthetic ACTH (Cosyntropin; Synacthen test) (Synacthène, Novartis, Basel, Switzerland). The choice of the 1 microgram Synacthen test over the 250 microgram was based on published studies showing that the higher dose is supraphysiologic and may miss mild cases of adrenal insufficiency.[19,20] Furthermore, the 1 microgram Synacthen test has already been validated in ICU patients.[12,21]

### *Assays*

Commercial assays were used for measurement of endocrine parameters: TSH, fT4 and T3 with electrochemiluminescence (Elecsys Systems, Roche Diagnostics, Mannheim, Germany), ACTH with an immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), PRL with chemiluminescence (Bayer Corporation, NY, USA), cortisol with an immunofluorometric assay (Chiron Corporation, East Walpole, MA, USA) and DHEAS with a radioimmunoassay (Coat-A-Count, Diagnostic

Products Corporation, CA, USA).

### *Statistical analysis*

Values of quantitative parameters that were either calculated (APACHE II, SOFA, ISS) or measured (all the endocrine function values) are presented as means ± SD, as well as median and range. Normality of distribution was assessed with Wilks-Shapiro's test. Qualitative measures (gender, presence of head trauma) are presented according to survival.

Comparisons of quantitative parameters between survivors/non-survivors were made with unpaired Student's t-tests and Wilcoxon's test (if their distribution was not normal). Comparisons of qualitative parameters between survivors/non-survivors were made with Fisher's exact test. Univariate logistic regression models of all the observed, calculated and measured parameters with survival/non-survival as the dependent variable were separately created. Multivariate logistic regression models were then created, using the same variables as in univariate logistic regression analysis plus composite variables (from a correlation matrix).[22] Models were sequentially

**Table 1.** Patients' pertinent data.

**a.** Qualitative patients' data by gender and head trauma vis-à-vis survival

| | Gender | | | | Trauma | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Head Trauma | | No head trauma | |
| | Survivors | Non-survivors | Survivors | Non-survivors | Survivors | Non-survivors | Survivors | Non-survivors |
| n | 75 | 8 | 8 | 3 | 56 | 7 | 27 | 4 |
| p value (Fisher's test) | 0.110 | | | | 1.00 | | | |

**b.** Results of quantitative patients' demographics and clinical assessment scores vis-à-vis survival

| | Age | | APACHE II | | SOFA | | ISS | |
|---|---|---|---|---|---|---|---|---|
| | Survivors | Non-survivors | Survivors | Non-survivors | Survivors | Non-survivors | Survivors | Non-survivors |
| Mean | 34.52 | 45.36 | 8.86 | 15.00 | 5.78 | 8.90 | 29.87 | 35.81 |
| SD | 15.16 | 23.62 | 3.80 | 6.97 | 2.50 | 3.47 | 10.51 | 7.09 |
| Median | 30.00 | 38.00 | 9.00 | 12.00 | 6.00 | 10.00 | 29.00 | 7.09 |
| Range | 17 to 82 | 18 to 79 | 1 to 16 | 9 to 32 | 0 to 12 | 4 to 15 | 9 to 66 | 25 to 50 |
| p value (Student's t-test) | | | <0.001 | | <0.001 | | 0.073 | |
| p value (Wilcoxon's test) | 0.135 | | | | | | | |

**c.** Results of univariate logistic regression and ROC analysis for quantitative patients' demographics and clinical assessment scores

| | Age | APACHE II | SOFA | ISS |
|---|---|---|---|---|
| **Univariate logistic regression** | | | | |
| b coefficient | 0.034 | 0.289 | 0.402 | 0.053 |
| SE of b coefficient | 0.017 | 0.098 | 0.130 | 0.030 |
| Constant | -3.369 | -5.312 | -4.949 | -3.754 |
| OR | 1.035 | 1.336 | 1.495 | 1.054 |
| 95% for OR | 1.000 to 1.071 | 1.102 to 1.619 | 1.157 to 1.932 | 0.993 to 1.118 |
| **ROC analysis** | | | | |
| Threshold (from ROC) | 65 | 8 | 9 | 33 |
| Sensitivity (%) | 36.4 | 100 | 54.5 | 81.8 |
| Specificity (%) | 93.9 | 49.4 | 92.8 | 61.4 |
| ROC AUC | 0.639 | 0.797 | 0.765 | 0.702 |
| 95% CI for ROC | 0.533 to 0.736 | 0.702 to 0.873 | 0.666 to 0.846 | 0.599 to 0.792 |

selected by a backwards stepwise process based on the likelihood ratio of survival/non-survival. Further selection of the models obtained was based on the Hosmer-Lemeshow chi-square goodness-of-fit criterion (according to this criterion, the better suited models have lower chi-square values and higher p probability values).[23] Finally, the predictive power of the univariate logistic regression models and of the selected multivariate models was assessed with receiver operating characteristic (ROC) plots; comparisons of ROCs were made based on their area under the curve (AUC).[24]

## RESULTS

Seventy-five of the 83 men and 8 of the 11 women survived and were transferred to medical or surgical hospital wards. Thirteen patients (11 survivors and 2 non-survivors) received dopamine infusion.

The APACHE II and SOFA scores were higher in non-survivors compared to survivors (Table 1). The overlap of these clinical severity scores was considerable between survivors and non-survivors. From the baseline endocrine evaluation, we found that survivors had higher PRL and DHEAS levels compared to non-survivors (Table 2). As with the clinical severity scores, the overlap between survivors and non-survivors was considerable. No significant differences between survivors and non-survivors were noted in the Synacthen or thyroid function tests. The presence of head trauma or dopamine administration was not significantly correlated with any of the hormonal parameters, whereas age was correlated with hormone levels (data not shown for simplicity; see below for further analysis of parameters with age).

The univariate logistic regression results were concordant with the comparisons carried out with the Student's, Wilcoxon's and Fisher's tests (Table 1). APACHE II, SOFA, ISS scores or DHEAS levels alone predicted ICU patients survival or death correctly in 85, 84, 83 and 84 of 94 cases, respectively. ROC plot analysis showed that, among the univariate parameters, the clinical severity scores and DHEAS were the most predictive (either with AUC of the ROC or the upper 95% CI of the ROC larger than 0.80). Among the many multivariate logistic regression models that were created, one that incorporated the APACHE II score and hormonal parameters (DHEAS and TSH*age) was well-fitted to assess survival/non-survival as an endpoint (with the Hosmer-Lemeshow chi-square goodness-of-fit criterion) (Table 3). Specifically, DHEAS and TSH*age contributed negatively to the logit probability of ICU death. This multivariate logistic regression model correctly predicted ICU survival or death correctly in 85 of 94 cases (as many as with the APACHE score alone). However, the corresponding ROC plot for this multivariate model had a much higher AUC compared to the AUCs of the ROCs obtained for APACHE II, SOFA or ISS scores alone. Consequently, this multivariate model was a better predictor of survival or death compared to APACHE II, SOFA or ISS scores alone (Table 3 and Figure 1).

## DISCUSSION

In this study of patients with trauma, survival prediction was better by combining the APACHE II score with age, TSH and DHEAS values than with the APACHE II score alone.

The mechanisms of endocrine changes in patients with trauma are not well known. For those with head trauma, anatomical abnormalities (vascular insult

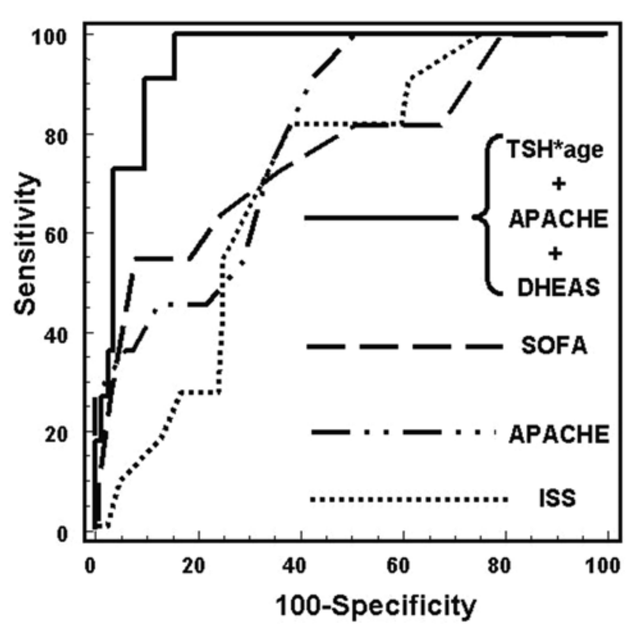


**Figure 1.** ROC plots for the final multivariate logistic regression model vs APACHE II, ISS and SOFA ROCs.

**Table 2.** Pertinent endocrine studies and statistical evaluation.

**a.** Results of thyroid function and prolactin assessment vis-à-vis survival

| | TSH | | T3 | | FT4 | | PRL | |
|---|---|---|---|---|---|---|---|---|
| | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** |
| Mean | 1.036 | 0.546 | 1.171 | 1.192 | 14.820 | 14.566 | 0.73098 | 0.46062 |
| SD | 1.259 | 0.495 | 0.312 | 0.292 | 6.948 | 3.208 | 0.55359 | 0.278955 |
| Median | 0.640 | 0.400 | 1.124 | 1.185 | 12.870 | 14.157 | 0.657 | 0.468 |
| Range | 0.0400 to 9.300 | 0.070 to 1.600 | 0.600 to 2.202 | 0.739 to 1.647 | 7.335 to 56.241 | 9.009 to 20.592 | 0.0135 to 4.104 | 0.063 to 1.044 |
| p value (Student's t-test) | | | 0.828 | | | | | |
| p value (Wilcoxon's test) | 0.079 | | | | 0.391 | | 0.037 | |

Units: TSH in mIU/L, T3 in nmol/L, FT4 in pmol/L, PRL in nmol/L

**b.** Results of univariate logistic regression and ROC analysis for thyroid function and prolactin evaluation

| | **TSH** | **T3** | **fT4** | **PRL** |
|---|---|---|---|---|
| **Univariate logistic regression** | | | | |
| b coefficient | -1.004 | 0.003 | -0.062 | -0.084 |
| SE of b coefficient | 0.708 | 0.023 | 0.051 | 0.047 |
| Constant | -1.308 | -2.286 | -1.929 | -0.949 |
| OR | 0.366 | 1.251 | 0.92 | 0.919 |
| 95% for OR | 0.091 to 1.469 | 0.168 to 9.301 | 0.898 to 1.099 | 0.846 to 1.008 |
| **ROC analysis** | | | | |
| Threshold (from ROC) | 0.24 | 1.14 | 11.84 | 10.9 |
| Sensitivity (%) | 45.5 | 63.6 | 81.8 | 72.7 |
| Specificity (%) | 86.7 | 54.2 | 38.6 | 69.9 |
| ROC AUC | 0.66 | 0.543 | 0.58 | 0.69 |
| 95% CI for ROC | 0.56 to 0.76 | 0.44 to 0.65 | 0.47 to 0.68 | 0.59 to 0.78 |

**c.** Results for corticotropin and adrenal function studies vis-à-vis survival

| | ACTH | | DHEAS | | Cortisol pre | | Cortisol post | | ΔCortisol | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** | **Survivors** | **Non-survivors** |
| Mean | 4.782 | 9.000 | 6.581 | 3.477 | 392.210 | 372.715 | 620.708 | 552.803 | 228.498 | 180.087 |
| SD | 3.548 | 13.141 | 2.919 | 1.494 | 188.695 | 262.280 | 202.920 | 261.957 | 124.832 | 119.863 |
| Median | 4.026 | 2.706 | 6.593 | 3.386 | 411.091 | 292.454 | 606.980 | 502.138 | 228.997 | 157.263 |
| Range | 0.198 to 17.556 | 0.220 to 36.608 | 0.964 to 13.217 | 0.607 to 5.597 | 8.277 to 882.880 | 49.662 to 824.941 | 237.274 to 1305.007 | 129.673 to 1012.553 | 8.277 to 620.775 | 5.518 to 358.670 |
| p value (student's t-test) | | | 0.001 | | 0.760 | | 0.317 | | 0.228 | |
| p value (Wilcoxon's test) | 0.564 | | | | | | | | | |

Units: ACTH in pmol/L, DHEAS in μmol/L, Cortisol in nmol/L

**d.** Results of univariate logistic regression and ROC analysis for corticotropin and adrenal function assessment

| | ACTH | DHEAS | Cortisol pre | Cortisol post | ΔCortisol |
|---|---|---|---|---|---|
| **Univariate logistic regression** | | | | | |
| b coefficient | 0.087 | -0.002 | -0.001 | -0.001 | -0.004 |
| SE of b coefficient | 0.044 | 0.001 | 0.001 | 0.001 | 0.003 |
| Constant | -2.578 | 0.430 | -1.825 | -1.057 | -1.293 |
| OR | 1.091 | 0.999 | 0.999 | 0.998 | 0.996 |
| 95% for OR | 1.001 to 1.190 | 0.997 to 0.999 | 0.996 to 1.002 | 0.995 to 1.001 | 0.990 to 1.002 |
| **ROC analysis** | | | | | |
| Threshold (from ROC) | 3.69 | 5597.10 | 297.97 | 549.04 | 80.01 |
| Sensitivity (%) | 72.7 | 100 | 63.6 | 63.6 | 36.4 |
| Specificity (%) | 54.2 | 63.9 | 69.9 | 61.4 | 89.2 |
| ROC AUC | 0.55 | 0.82 | 0.59 | 0.59 | 0.59 |
| 95% CI for ROC | 0.45 to 0.66 | 0.73 to 0.89 | 0.46 to 0.67 | 0.48 to 0.69 | 0.49 to 0.69 |

in the hypothalamic-pituitary area or basal skull fractures)[25] or functional alterations related to brain edema, elevated intracranial pressure,[5,26] hypotensive and/or hypoxic insults[27] and cytokines, in particular interleukin-6,[28] have all been implicated.

Prolactin rises in the acute phase of critical illness; this rise has been attributed to the actions of vasoactive intestinal polypeptide, oxytocin or cytokines.[29] Higher PRL has been noted in trauma patients compared to other ICU patients.[5,30] In our study PRL was not included in the final predictive model; however, we found higher PRL levels in survivors compared to non-survivors. The possible association between PRL and survival and the mechanism involved warrants further investigation.[31-35]

**Table 3.** Selected multivariate logistic regression model

| | Multivariate model |
|---|---|
| Logistic regression | |
| Chi square goodness-of-fit | 2.67 |
| Chi square p | 0.952 |
| Parameters in models | |
| Constant | -1.713 |
| APACHE II ± SE (p) | 0.360 ± 0.120 (0.002) |
| OR (95% CI) | 1.431 (1.132 to 1.809) |
| DHEAS ± SE (p) | -0.002 ± 0.0008 (0.006) |
| OR (95% CI) | 0.997 (0.996 to 0.999) |
| TSH*Age ± SE (p) | -0.048 ± 0.025 (0.054) |
| OR (95% CI) | 0.953 (0.907 to 0.9999) |
| ROC analysis | |
| Sensitivity (%; from ROC) | 100 |
| Specificity (%; from ROC) | 84.2 |
| ROC AUC | 0.952 |
| 95% CI for ROC | 0.887 to 0.985 |

p of ROC AUCs comparisons: Multivariate model vs APACHE: p=0.028; vs ISS: p=0.013; vs SOFA: p=0.024

Regarding the pituitary-thyroid axis, conflicting results have been presented vis-à-vis survival in patients in critical condition.[36] In some studies, low or high TSH and low T3 or low T4 have been associated with higher mortality,[37-41] while other studies have not found any such association.[42,43] Moreover, in a study of multiple trauma patients, low T4 was associated with higher mortality.[40] In our study overall thyroid function was within normal limits; however, the factor of TSH*age was negatively associated with mortality. This may possibly indicate that the condition of these patients is improving, since it is known that in critically ill patients a high TSH is an indication of recovery from "non-thyroidal illness" ("euthyroid sick syndrome").[44,45]

Cortisol rises in trauma and/or sepsis, probably to counteract the inflammatory cytokine response to such conditions.[46] Studies examining the prognostic value of baseline and Synachten-stimulated serum cortisol in critically ill patients have failed to demonstrate a reproducible correlation between cortisol responses and outcome.[9] Both high and low cortisol levels have been associated with higher mortality, whereas others showed that cortisol levels failed to predict clinical outcome.[9] In our patients with multiple trauma, neither pre- or post-Synacthen cortisol nor

Δcortisol levels contributed to the final (best) logistic regression model. These parameters were removed according to the likelihood ratio-based backwards stepwise process and the Hosmer-Lemeshow chi-square goodness-of-fit criterion (detailed data were not shown in the results section for simplicity).

The profile of DHEAS has not been studied as extensively as that of cortisol in critical illness.[9] In certain studies DHEAS was found to be lower in ICU patients compared to healthy individuals;[10,47] this has been attributed to a shift of steroidogenesis to cortisol production by critical illness.[48] Significantly higher DHEAS levels were noted in our trauma survivors than in non-survivors and DHEAS was included in the logistic regression model. The association of high DHEAS with lower mortality found in our study might be explained by its immunoenhancing properties, since it has been shown that DHEA, the most plentiful steroid hormone, activates the monocyte-macrophage system, antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation, exerts a direct immunostimulatory effect on murine T cells and increases cytokine production. Nevertheless, the relevant clinical findings are considered to be controversial.[9,10,48-52]

The number of patients who did not survive in our study was relatively small and this constitutes a limitation. This could also explain the lack of statistical significance in the other hormone levels between survivors and non-survivors. Clearly, further investigation in a larger cohort is needed to better define endocrine predictors in polytraumatized, critically ill patients in order to assess the utility – if any – of such predictors in the clinical management of these patients.

In conclusion, in critically ill patients with trauma, age, TSH and DHEAS levels upon admission to the ICU, in combination with the APACHE II score, may predict outcome more accurately than the APACHE II score alone.

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