ORIGINAL ARTICLE

Association of serum prolactin levels and thyroid hormones with poisoned patient outcome

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Abstract

Background: In acute and chronic phases of severe diseases, endocrine changes occur. Some hormones, such as prolactin (PRL) and thyroid hormones, were considered predictors of ICU patients' outcomes. The present study evaluates thyroid hormone profile, serum PRL level, and their relationship with ICU poisoned patients' mortality rate.

Methods: This study included 140 inpatients in the Toxicology Intensive Care Unit (TICU) who enrolled in a prospective study of a single center and observational.

After admission to the ICU, the researchers collected venous blood samples from all patients directly. Concurrently, the APACHE II score was calculated. The collected samples analysis was performed based on the entire triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), and PRL level.

Results: One hundred and forty subjects were studied, of which 109 (75.85%) were male with a mean age of 34.17 ± 14.01. One hundred and eighteen patients were survivors with a mean age of 33.29 ±13.76. In contrast, 22 patients with a mean age of 38.91 ±14.69 died. The model of PRL combined with APACHE II score (OR 1.17, 95% CI 1.06 to 1.28, *P-value* =0.001) was the best model for predicting post-ICU mortality in our study.

Conclusions: This study's results are consistent with the previous research, indicating a higher incidence of thyroid and PRL hormone changes in patients hospitalized in the ICU.

It can be concluded that the presence of PRL based on the APACHE II score can lead us to be more precise in predicting the outcome of poisoning in hospitalized patients.

Keywords: APACHE II score, Mortality, Prolactin, Thyroid hormones.

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INTRODUCTION

The Global load of Disease in 2017 showed that almost 72,400 deaths worldwide could be due to poisoning (intentional or accidental) (1). The most widely used ICU outcome measurement is the mortality rate ranging from 20 to 30% (2,3). The Stability and Workload Index for Transfer (SWIFT), the ICU discharge readiness, the Minimizing ICU Readmission, and Acute Physiology and Chronic Health Evaluation (APACHE) II are considered the various scoring methods to predict ICU mortality. However, their beneficial values for the decline in mortality remain a matter of debate (4). Since endocrine changes in the acute and chronic phases of severe diseases take place (5,6), in some studies, endocrine hormones such as prolactin (PRL) and thyroid hormones were considered as predictors of ICU patients' outcomes (7,8). PRL is a hormone/cytokine synthesized and secreted in the anterior pituitary. It can also be produced in extra-pituitary regions, including the mammary epithelium, uterus, immune system, etc.(9). Due to the PRL receptor's expression over immune cells, this hormone can be pro- or anti-inflammatory by regulating inflammatory mediators (10,11).

The regulatory activity of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) secreted from the thyroid gland, comprising thyroid hormones: Triiodothyronine (T3) and thyroxine (T4) (12,13).

Thyroid hormones have a vital role in maintaining homeostasis, energy consumption, metabolism, and activity of cells. These hormones affect the cardiovascular, neurotic, muscular, skeleton, and other systems (14). According to the previous studies, the thyroid hormones concentration serum is altered in the chronic stage of severe disease due to decreased thyroid-stimulating hormone (6,15,16). The present study evaluates thyroid hormone profile, serum PRL level, and their relationship with the mortality proportion of ICU poisoned patients.

METHODS

Study design

This prospective observational study was conducted at the

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Toxicological Intensive Care Unit (TICU) of Loghman-Hakim Hospital Poison Center (LHHPC). A total of 140 patients admitted to our TICU with different poisoning were enrolled. One hundred and forty patients hospitalized in the TICU with various poisonings were included in the study.

Exclusion criteria included concomitant therapy along with medications, influencing hypothalamic-pituitary activity, including etomidate, diphenylhydantoin, or rifampicin, and an endocrine disorder, which already existed.

An appropriate questionnaire was prepared based on demographic data (age, sex), type of poisoning, lab tests (total T3, total T4, TSH, PRL), and patient outcomes. Written informed consent was obtained from patients or their families to participate in the study. The Ethics Committee of the Vice-Chancellor for Research of Shahid Beheshti University of Medical Sciences, Tehran, Iran, approved the protocol of this study.

Assay

Immediately after hospitalization to the ICU, venous blood samples were collected from all patients once. Concurrently, the score was calculated using the APACHE II scoring method, utilizing 12 physiological variables, age, and chronic health.

The electrochemiluminescence immunoassay (ECLIA) method (Modular Analytics E170, Roche, America) measured total T3, total T4, TSH, and the ECLIA method (Elecsys 2010, Roche, America) measured PRL from blood samples.

In the laboratory, the ranges of regular references for thyroid hormones and PRL are as follows: TSH (0.3–4.6 mIU/L), T3 (67–156 ng/ dL), T4 (4.5–11.6 μg/dL), and prolactin (0–15 ng/mL males, 0–25 females). Hormone results are considered to range from normal to abnormal (high or low) for any deviation.

Statistical analysis

SPSS software (version 16, Chicago, IL, USA) was used to analyze the statistical data. In this study, patients were divided into two groups: survivors and non-survivors. The nominal (percent) and numeric variables were represented as the mean and standard deviation. The $\chi 2$ test or Fisher's exact test and other quantitative variables were used to compare the categorical variables with the student's t-test or Mann-Whitney U test. All elements with survivors and non-survivors as the dependent variables were independently formed using univariate and multivariate logistic regression models. To evaluate the model fit, the present study used the Hosmer-Lemeshow goodness-of-fit test. The odds ratio (OR) with 95% confidence interval (95% CI) and statistically significant p-value of ≤ 0.05 were considered. Lastly, receiver operating characteristic (ROC) plots and the univariate logistic regression models' predictive power and the selected multivariate models were evaluated. ROCs were compared according to the area under the curve (AUC).

RESULTS

One hundred and forty subjects were studied, of which 109 (75.85%) were male with a mean age of 34.17 ± 14.01. One hundred and eighteen patients were survivors with a mean age of 33.29 ±13.76. In contrast, 22 patients with a mean age of 38.91 ±14.69 were non-survivors.

Crude odds ratio (95% CI) obtained by analysis of for age and sex 1.03 (0.99-1.06) and 0.55 (0.20-1.49) for survivors and non-survivors, respectively. The crude odds ratio (95% CI) obtained in the analysis of survivors and non-survivors groups were significant for APACHE-II and PRL. The *P* values were <0.0001 and 0.006, respectively. (See Table 1)

According to Table 1, no significant difference was observed between the two groups in thyroid hormones (P-value> 0.05). Therefore, thyroid tests may not be a good predictor of mortality in our TICU patients. The mean ± SD APACHE II score of the survivors and non-survivors was 18.59 ± 6.75 and 13.70 ± 5.37, respectively. The median PRL levels in the survivors and non-survivors were 441.00 (285.95-1126.75) and 390.30 (272.42-642.55), respectively.

Table 1. Characteristics of ICU survivors and non-survivors patients and crud odds ratio

	Total (n= 140)	Survivors (n= 118)	non- survivors (n=22)	P value*	Odds ratio (95% Cl)
Age	34.17 (14.01)	33.29 (13.76)	38.91 (14.69)	0.084	1.03 (0.99-1.06)
Sex (men)	109 (77.85)	94(79.66)	15(68.18)	0.234	0.55 (0.20-1.49)
APACHE II score	14.47 (5.86)	13.70 (5.37)	18.59 (6.75)	<0.0001	1.15 (1.06-1.26)
Hospital stay (day)	5 (3-7)	5 (3-7)	5 (3-9)	0.616	1.05 (0.98-1.12)
Prolactin	407.30 (274.12-680.20)	390.30 (272.42-642.55)	441.00 (285.95-1126.75)	0.006	1.01 (1.00-1.02)
Hormone levels					
T3	1.00 (0.80-1.50)	1.10 (0.8-1.50)	1.11 (0.77-1.55)	0.904	1.01 (0.38-2.63)
T4	7.30 (6.10-8.85)	7.30 (6.20-8.92)	7.25 (4.82-8.67)	0.277	0.83 (0.67-1.03)
TSH	0.90 (0.60-1.37)	0.80 (0.60-1.20)	1.10 (0.57-2.15)	0.153	1.17 (0.98-1.41)

- Data were presented with mean (SD) for normal variables and median (25th—75th percentile) for non-normal variables, sex were presented with frequency (percent).
- *P value* for comparing survived and died groups, t-student test was used for continuous variables (Mann-Whitney tests for continuous variables not normally distributed) and X^2 tests were used for categorical variables.

All three models obtained by logistic regression presented significant *P* value (< 0.05); however, model 3 (PRL combined with APACHE II score) possessed the lowest Chi-square for the Hosmer Lemeshow test, as well as the highest AUC of the ROC to predict outcomes. (See Table 2)

The AUC of the ROC of the PRL to predict post-ICU mortality was 0.557 (95% CI 1.00 to 1.02, P-value =0.024). Moreover, its cut-off point of 1120 had a sensitivity of 95% and a specificity of 27% (Figure 1).

As shown in Figure 2, the model of PRL combined with the APACHE II scoring model (OR 1.17, 95% CI 1.06 to 1.28, P-value =0.001) was the best model to predict post-ICU mortality in this research.

The poisoning type of the studied patients is shown in Table 3, the most poisoning included aluminum phosphide (ALP) 14.3%, methadone 12.1, and MDT 12.1%, and in 12.8% of the cases, the cause was unknown. No significant differences were observed between prolactin levels and type of intoxication.

DISCUSSION

As mentioned above, attention to the patients admitted to ICU and the prediction of their outcome is particularly desirable. The current research findings revealed that combining the APACHE II scoring model with the PRL level was the best model for predicting mortality. Accordingly, PRL levels were statistically higher in non-survivors than survivors, and logistic regression analysis was also significant.

Still, thyroid hormones (TSH. T4. T3) did not significantly differentiate survivors' non-survivors. According to the obtained results, low T3 (100% of patients) was the most joint abnormality. However, T4 and TSH levels were normal in 91.4% and 85.7% of patients, respectively. In line with the literature, thyroid hormone levels endure fluctuation in the acute and chronic phases of severe disease (17), which means two h after surgery or trauma, a decline in T3 levels and fleetingly development in T4 and TSH levels are observed

Table 2. Logistic regression models predicting mortality in the ICU and their Area under ROC curve and Hosmer lemeshow test

	OR	95% CI	*P* value	Area under ROC curve	Chi-square for Hosmer lemeshow test	Hosmer-Lemeshow *P* value
Model1						
Prolactin	1.01	1.00-1.02	0.024	0.575	7.05	0.531
Model2						
APACHE II score	1.15	1.06-1.26	0.001	0.716	10.33	0.242
Model3						
APACHE II score	1.17	1.06-1.28	0.001	0.752	3.85	0.87
Prolactin	1.01	1.00-1.02	0.025			

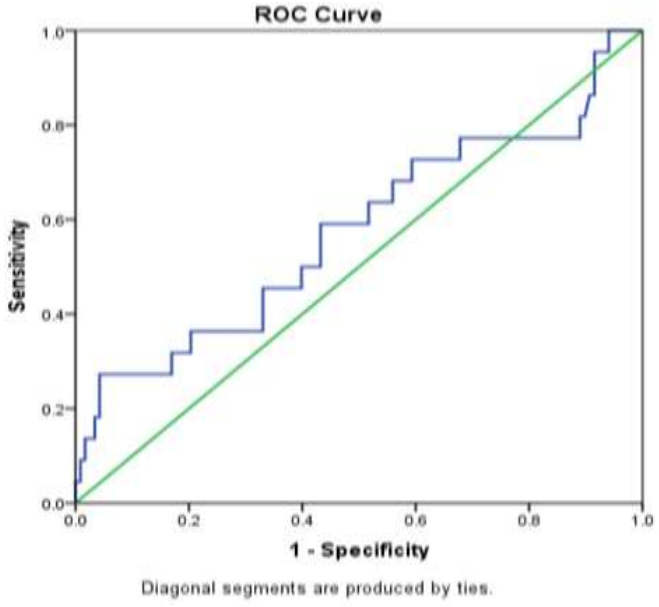

Figure 1. The area under the ROC curve of the PRL for predicting ICU mortality

Table 3. Type of poisoning in studied patients

Type of poisoning	Frequency (%)
Cardiovascular medicines	3 (2.1%)
Methanol	4 (2.9%)
Tramadol	15 (10.7%)
Methadone	17 (12.1%)
Toxin	3 (2.1%)
Anti-Depressant	5 (3.6%)
Anti-Convulsive	4 (2.9%)
BZD (Benzodiazepines)	11 (7.9%)
Opium	14 (10%)
ALP (Aluminum phosphide)	20 (14.3%)
Amphetamine	7 (5%)
CO (Carbon Monoxide)	2 (1.4%)
MDT	17 (12.1%)
Unknown	18 (12.8%)

(18). At that stage, a reduced peripheral alteration of T4 to T3 leads to low T3 levels (sick euthyroid syndrome) (19). Therefore, TSH and T4 levels often shift to normal, while T3 levels are low, indicating a self-protective adaptation to illness. (15) Kumar et al., in prospective research, including 100 patients admitted to ICU, T3 in 61%, T4 in 14%, and TSH in 7% of patients reported to be low, respectively. (20).

Also, Kanj et al. studied 70 patients and reported low T3 concentrations in all patients, low T4 in 22 (31%), and low TSH in 2 (2.9%) (21). Moreover, in the present study, no thyroid hormone levels appeared as a predictor of ICU mortality than Kumar et al., as well as some other studies (21–24). However, Mazzeo et al. 's study confirmed our findings, which reported thyroid axis suppression in 57% of patients and no correlation between thyroid hormones and outcomes (25).

Elevated PRL level was detected in all patients studied. Among them, there were 118 survivors and 22 non-survivors. A positive correlation was perceived between mortality rate and PRL level. In our study, PRL, either individually or combined with the APACHE II scoring model, was significantly identified as a mortality predictor in TICU. It has been suggested that a rise in PRL levels is seen in the first days after the occurrence of a critical illness (26,27). As members of neuroendocrine axes, oxytocin, TRH, and vasoactive intestinal peptide (VIP) affect PRL secretion and lead to PRL rise in stressful conditions (28). Moreover, PRL plays an immunomodulatory role in the physiological and pathological conditions by its receptors expressed on B and T lymphocytes.

According to the evidence, throughout the illness phase, hyperprolactinemia may contribute to the immune cascade (29). This study's results are consistent with the previous studies, indicating hyperprolactinemia in more than 50% of patients in the early and acute stage of a critical illness.

Olivecrona et al., in a prospective study of 45 patients, reported elevated levels of serum PRL in 48.3% of the men and 66.7% of the women at day one after traumatic brain injury and inconsistently. Thus, they found no significant difference between deceased/alive individuals in terms of the PRL levels (30).

Mazzeo et al. evaluated 113 patients with different critical illnesses, including Acute Respiratory Distress Syndrome (ARDS), severe Traumatic Brain Injury (TBI), Subarachnoid Hemorrhage (SAH), and patients with neurological disease at the time of Brain Death (BD). PRL levels were significantly increased by 67% of ARDS patients. Thyroid axis suppression has been shown to be the most common change. In contrast, the strongest mortality predictor was activating the hypothalamic-pituitary-adrenal axis independent of the underlying medical condition (25).

Research on ICU patients at Loghman Hakim Hospital during 2013-2014 showed assessing the predictive power of cortisol and thyroid hormones. Two hundred patients were evaluated for thyroid hormone levels, cortisol, type of poisoning, clinical signs and symptoms, and other factors. The most common cause of poisoning was reported opioids (39%). The relationship between thyroid hormones and cortisol and patients' blood pressure was measured, but no significant difference was found. Examination of these factors in patients poisoned with aluminum phosphide showed that cortisol was significantly higher in this group. Finally, it was reported that among the elements, cortisol is the better predictor factor (31). the current study focused on prolactin and thyroid hormones. Thyroid hormones data in our study were close to the previous research, and we also found that these hormones are not a good factor in predicting mortality in patients.

The study's findings also revealed that the APACHE II scoring model's discriminatory ability to predict mortality is significantly better than the PRL level. (0.716 [95% CI 1.06 to 1.26] versus 0.575 [95% CI 1.00 to 1.02], P-value =0.001). In line with the present study, previous reports revealed that the admission APACHE II score was related to ICU readmission and post-ICU mortality (32–34).

CONCLUSION

The obtained data confirm that previous studies indicated a high incidence of thyroid and PRL hormone changes in critically ICU patients. It can be concluded that the presence of PRL, and the APACHE II scoring model, can precisely lead us to predict poisoning outcomes in hospitalized patients. Thyroid tests and PRL alone did not have a predictive role in our poisoned patients' outcome, contrary to previous studies performed on ICU patients admitted for any reason except poisoning. This could probably be due to the nature of their illness in the chronic phase; however, our patients were in an acute phase of poisoning.

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REFERENCES

1. Abubaker Z, Nisar M, Jamshed A, Abbas M, Hashmi K, Arsalan M. A Retrospective Analysis on Poison Related Mortalities in a Tertiary Care Centre in Pakistan. Asia Pacific J Med Toxicol. 2020;9(3):85–90.
2. Yang S, Wang Z, Liu Z, Wang J, Ma L. Association between time of discharge from ICU and hospital mortality: a systematic review and meta-analysis. Crit Care. 2016;20(1):1–15.
3. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system: risk prediction of hospital mortality for critically III hospitalized adults. Chest. 1991;100(6):1619–36.
4. Lee H, Lim CW, Hong HP, Ju JW, Jeon YT, Hwang JW, et al. Efficacy of the APACHE II score at ICU discharge in predicting post-ICU mortality and ICU readmission in critically ill surgical patients. Anaesth Intensive Care. 2015;43(2):175–86.
5. Van den Berghe G, Wouters P, Weekers F, Mohan S, Baxter RC, Veldhuis JD, et al. Reactivation of pituitary hormone release and metabolic improvement by infusion of growth hormone-releasing peptide and thyrotropin-releasing hormone in patients with protracted critical illness. J Clin Endocrinol Metab. 1999;84(4):1311–23.

6. Van den Berghe G. Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin. 2003;32(2):385–410.
7. Ilias I, Stamoulis K, Armaganidis A, Lyberopoulos P, Tzanela M, Orfanos S, et al. Contribution of endocrine parameters in predicting outcome of multiple trauma patients in an intensive care unit. HORMONES-ATHENS-. 2007;6(3):218.
8. Akbaş T, Deyneli O, Sönmez FT, Akalın S. The pituitary–gonadal–thyroid and lactotroph axes in critically ill patients. Endokrynol Pol. 2016;67(3):305–12.
9. Harris J, Stanford PM, Oakes SR, Ormandy CJ. Prolactin and the prolactin receptor: new targets of an old hormone. Ann Med. 2004;36(6):414–25.
10. Legorreta-Haquet M V, Chávez-Rueda K, Montoya-Díaz E, Arriaga-Pizano L, Silva-García R, Chávez-Sánchez L, et al. Prolactin down-regulates CD4+ CD25hiCD127low/- regulatory T cell function in humans. J Mol Endocrinol. 2012;48(1):77.
11. López-Rincón G, Mancilla R, Pereira-Suárez AL, Martínez-Neri PA, Ochoa-Zarzosa A, Muñoz-Valle JF, et al. Expression of autocrine prolactin and the short isoform of prolactin receptor are associated with inflammatory response and apoptosis in monocytes stimulated with Mycobacterium bovis proteins. Exp Mol Pathol. 2015;98(3):517–26.
12. Mullur R, Liu Y-Y, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev. 2014;94(2):355–82.
13. Ortiga- Carvalho TM, Chiamolera MI, Pazos- Moura CC, Wondisford FE. Hypothalamus- pituitary- thyroid axis. Compr Physiol. 2011;6(3):1387–428.
14. Rashidi MA, MAHABADI HA, Khavanin A. Evaluation of the effects of chronic exposure to organophosphorus pesticides on thyroid function. Asia Pacific J Med Toxicol. 2020;9(2):35–43.
15. Economidou F, Douka E, Tzanela M, Nanas S, Kotanidou A. Thyroid function during critical illness. Hormones. 2011;10(2):117–24.
16. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin North Am. 2007;36(3):657–72.
17. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. lancet Diabetes Endocrinol. 2015;3(10):816–25.
18. Michalaki M, Vagenakis AG, Makri M, Kalfarentzos F, Kyriazopoulou V. Dissociation of the early decline in serum T3 concentration and serum IL-6 rise and TNFα in nonthyroidal illness syndrome induced by abdominal surgery. J Clin Endocrinol Metab. 2001;86(9):4198–205.
19. Van den Berghe G. Non-thyroidal illness in the ICU: a syndrome with different faces. Thyroid. 2014;24(10):1456–65.
20. Kumar KVSH, Kapoor U, Kalia R, Chandra NSA, Singh P, Nangia R. Low triiodothyronine predicts mortality in critically ill patients. Indian J Endocrinol Metab. 2013;17(2):285.
21. Kanji S, Neilipovitz J, Neilipovitz B, Kim J, Haddara WMR, Pittman M, et al. Triiodothyronine replacement in critically ill adults with non-thyroidal illness syndrome. Can J Anesth Can d'anesthésie. 2018;65(10):1147–53.
22. Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3, 3′, 5′-triiodothyronine (rT3) and 3, 5, 3′-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. J Clin Endocrinol Metab. 2005;90(8):4559–65.
23. Meyer S, Schuetz P, Wieland M, Nusbaumer C, Mueller B, Christ-Crain M. Low triiodothyronine syndrome: a prognostic marker for outcome in sepsis? Endocrine. 2011;39(2):167–74.
24. El-Ella SSA, El-Mekkawy MS, El-Dihemey MA. Prevalence and prognostic value of non-thyroidal illness syndrome among critically ill children. An Pediatría (English Ed. 2019;90(4):237–43.
25. Mazzeo AT, Guaraldi F, Filippini C, Tesio R, Settanni F, Lucchiari M, et al. Activation of pituitary axis according to underlying critical illness and its effect on outcome. J Crit Care. 2019;54:22–9.
26. Nguyen DN, Huyghens L, Schiettecatte J, Smitz J, Vincent J-L. High prolactin levels are associated with more delirium in septic patients. J Crit Care. 2016;33:56–61.
27. Téblick A, Langouche L, Van den Berghe G. Anterior pituitary function in critical illness. Endocr Connect. 2019;8(8):R131–43.
28. Van den Berghe G. Novel insights into the neuroendocrinology of critical illness. Eur J Endocrinol. 2000;143(1):1–13.
29. Savino W. Prolactin: an immunomodulator in health and disease. Endocr Immunol. 2017;48:69–75.
30. Olivecrona Z, Dahlqvist P, Koskinen L-OD. Acute neuro-endocrine profile and prediction of outcome after severe brain injury. Scand J Trauma Resusc Emerg Med. 2013;21(1):1–13.
31. Frost SA, Alexandrou E, Bogdanovski T, Salamonson Y, Davidson PM, Parr MJ, et al. Severity of illness and risk of readmission to intensive care: a meta-analysis. Resuscitation. 2009;80(5):505–10.
32. Yalçın M, Gödekmerdan E, Tayfur K, Yazman S, Ürkmez M, Ata Y. The APACHE II score as a predictor of mortality after open heart surgery. Turkish J Anaesthesiol Reanim. 2019;47(1):41.
33. Lee JH, Hwang SY, Kim HR, Kim YW, Kang MJ, Cho KW, et al. Effectiveness of the sequential organ failure assessment, acute physiology and chronic health evaluation II, and simplified acute physiology score II prognostic scoring systems in paraquat-poisoned patients in the intensive care unit. Hum Exp Toxicol. 2017;36(5):431–7.