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The Gender Difference of Routine Laboratory Tests Performance in Prediction of Early Mortality in Ischemic Stroke Patients

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ABSTRACT

Objective: Despite improvements in the treatment and management of ischemic stroke patients, early mortality rates remain high. Identification of high-risk patients may permit effective and more intensive interventions for good outcome. Routine laboratory tests may help predict high risk patients. So we re-evaluated the predictive power of the laboratory tests for assessing early mortality by focusing on the gender differences.

Methods: We retrospectively analyzed the demographic data, laboratory findings and mortality reports of the ischemic stroke patients using SPSS statistical package version 23.0. The differences of variables were determined between patients with and without early mortality via Student's T and Mann Whitney tests. Univariate and multivariate logistic regression analysis were performed to evaluate the predictive value of the laboratory tests.

Results: The 30 day mortality rate was 16 percent and the predictive power of laboratory tests was different between male and female. Multivariate regression analysis indicated that age and serum urea levels could predict early mortality in both genders. The age cut-off value for the prediction of early mortality was 57.5 and 68.5 years in male and female patients respectively. The elevation of serum urea levels higher than 51.5 and 48.5 mg/dl associated with higher early mortality rate in male and female patients respectively. Furthermore, lymphocyte count, low-density lipoprotein cholesterol, total cholesterol, fast blood sugar and hemoglobin levels independently predict early mortality in female but not in male patients.

Conclusions: Age and serum urea levels may be considered as useful biomarkers for the prediction of the early mortality rates in ischemic stroke patients. The predictive power of other laboratory tests was gender-dependent.

Keywords: Laboratory tests, ischemic stroke, early mortality, gender

ÖZET

İskemik İnme Hastalarındaki Erken Ölümün Öngörülmesinde Rutin Laboratuar Test Sonuçlarının Cinsiyetler Arasındaki Farklılaşması

Amaç: İskemik inme hastalarının tedavisinde ve yönetimindeki gelişmelere rağmen, erken dönemde mortalite oranları yüksektir. Yüksek riskli hastaların belirlenmesi, iyi sonuç almak için etkili ve daha yoğun müdahalelere izin verebilir. Rutin laboratuvar testleri yüksek riskli hastaları öngörmede yardımcı olabilir. Bu nedenle, cinsiyete bağlı farklılıkları dikkate alarak erken ölüm oranlarını değerlendirmek için yapılan laboratuvar testlerinin öngörme gücünü yeniden değerlendirdik.

Yöntem: İskemik inme hastalarının demografik verileri, laboratuvar bulguları ve mortalite raporlarını SPSS istatistik paket versiyon 23.0 kullanarak geriye dönük olarak analiz ettik. Değişkenlerin farklılıkları erken mortalite olan ve olmayan hastalar arasında Student's T ve Mann Whitney testleri ile belirlendi. Laboratuvar testlerinin prediktif değerini değerlendirmek için tek değişkenli ve çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: 30 günlük mortalite oranı % 16 idi ve laboratuar testlerinin öngörme gücü kadınlar ile erkekler arasında farklılık gösteriyordu. Çok değişkenli regresyon analizi, yaş ve serum üre seviyelerinin her iki cinsiyette de erken mortaliteyi öngörebileceğini gösterdi. Erken mortalite tahmini için yaş kesme değeri, erkek ve kadın hastalarda sırasıyla 57,5 ve 68,5 idi. Serum üre seviyelerinin erkek ve kadın hastalarda sırasıyla 51,5 ve 48,5 mg / dl'den yüksek olması yüksek mortalite oranı ile ilişkili bulunmuştur. Ayrıca, lenfosit sayısı, düşük dansiteli lipoprotein kolesterol, total kolesterol, hızlı kan şekeri ve hemoglobin düzeyleri kadınlarda erken ölüm oranını bağımsız olarak öngörürken, erkek hastalarda öngörmemektedir.

Sonuç: Yaş ve serum üre düzeyleri iskemik inme hastalarında erken ölüm oranlarının öngörülmesinde yararlı bir biyobelirteç olarak düşünülebilir. Diğer laboratuar testlerinin öngörme gücü ise cinsiyete bağlı olarak değişmektedir.

Anahtar sözcükler: Laboratuar testleri, iskemik inme, erken ölüm, cinsiyet

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INTRODUCTION

Ischemic stroke is defined as a neurological event occurring suddenly and lasting more than 24 hours.[1] In most cases, ischemic stroke leads to the early mortalities and severe disabilities in the patients.[2] The risk of cerebral vascular such as ischemic stroke and final patient's outcome are gender-dependent. Gender affects the clinical findings, response to treatment and the final outcome in the ischemic stroke patients.[3] The etiology of this observation may relate to sociocultural factors, hormonal and/or gender-associated molecular differences.[4,5] So patient's gender should be considered as a key variable in the prognosis of early mortalities. Good performance in the prediction of early mortality provides the opportunities for the appropriate clinical approach to care and manage high risk patients.[6] previous studies proposed several models to predict early mortality in ischemic stroke patients.[7-9] In clinical setting, the predictors must have high predictive power and be simple and affordable. Thus, routine laboratory tests may be suitable for this purpose. There are several studies trying to find sensitive and specific biomarkers for prediction of early mortality. They proposed laboratory tests as predictors.[10-11] For most laboratory tests, the normal ranges are different between male and female. Therefore, it is possible that the laboratory tests can predict the early mortality in a gender-dependent manner. The aim of this study is to re-evaluate the predictive power of the laboratory tests for early mortality prognosis by focusing on gender differences.

Table 1. Characteristics of male patients

	Male		
Variable	Alive	Death	P value
1 Age	66.30±14.79	72.87±12.14	0.0001
2 FBS (mg/dL)	126.86±71.84	142.93±89.70	0.066
3 BS (mg/dL)	156.82±88.64	167.36±96.52	0.269
4 LYM (%)	23.33±13.55	13.84 ± 12.01	0.0001
5 WBC (count/ul)	8402.81±3202.88	10824.28±5701.71	0.0001
6 NET (%)	68.09±15.65	79.70 ± 10.91	0.0001
7 PLT (count/ul)	207.13±74.43(*10^3)	208.31± 105.23(*10^3)	0.055
8 HB (g/dL)	13.06±2.27	12.38±2.49	0.009
9 RBC (count/ul)	4.660±0.693(*10^6)	4.369±0.983(*10^6)	0.001
10 HCT (%)	40.42±5.82	38.44±12.82	0.003
11 LDLc (mg/dL)	100.34±38.37	113.06±42.25	0.002
12 CHL (mg/dL)	185.37±49.50	199.89±55.31	0.014
13 TG (mg/dL)	151.63±71.39	155.60 ± 76.82	0.549
14 HDLc (mg/dL)	44.94±13.94	46.30±15.57	0.294
15 Urea (mg/dL)	47.94±33.40	65.26±49.37	0.0001
16 CRT (mg/dL)	1.15±0.591	1.36±0.922	0.006
17 PLR	14.36±20.58	29.28±42.62	0.0001
18 NLR	5.34± 7.93	12.14±15.39	0.0001
19 LHR	2.38±1.00	2.66±1.32	0.072

MATERIALS AND METHODS

Data collection

In this retrospective study, after ethical approval, we reviewed medical records of 1572 patients with confirmed ischemic stroke who had been admitted to Imam Khomeini Hospital of Urmia from 2006 to 2016. The first laboratory findings after admission were analyzed including fasting blood sugar (FBS), blood sugar (BS), lymphocyte (LYM), white blood cells (WBCs), neutrophils (NET), platelets (PLT), hemoglobin (HB), Red blood cells (RBCs), hematocrit (HCT), low-density lipoprotein cholesterol (LDLc), cholesterol (CHL), triglyceride (TG) , High-density lipoprotein cholesterol (HDLc), Urea, Creatinine (CRT), platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), LDLc/HDLc Ratio (LHR). The mortality in the first 30 days after ischemic stroke was considered as the early mortality.

Statistical analysis

The collected data were analyzed by SPSS statistical package version 23.0 and the descriptive analysis was used to determine mean ± SD of variables. The normality of the variables was checked with the Kolmogorov-Smirnov normality tests, Student-t and Mann-Whitney tests were used to estimate differences of mean of variables between patients with and without early mortality. Univariate and multivariate logistic regression analysis were performed to evaluate the predictive power of the laboratory tests. The area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated (AUC with 95% CI). The AUC higher than 0.6 was considered as the acceptable predictive value to predict early mortality. Sensitivity and specificity at the optimal cut-off points

Table 2. Characteristics of female patients

	Female		
Variable	Alive	Death	P value
1 Age	65.27±14.69	74.46±11.95	0.0001
2 FBS (mg/dL)	128.62±66.81	164.80±90.91	0.0001
3 BS (mg/dL)	158.25±97.72	188.55±91.62	0.0001
4 LYM (%)	24.36±12.62	17.93±14.96	0.0001
5 WBC (count/ul)	8134.99±3041.93	11898.77±13716.42	0.0001
6 NET (%)	67.65± 14.35	75.48±16.41	0.0001
7 PLT (count/ul)	231.94±81.40(*10^3)	213.53±98.80(*10^3)	0.001
8 HB (g/dL)	12.41±1.55	12.16 ±5.37	0.0001
9 RBC (count/ul)	4.446± 0.633(*10^6)	4.160±0.633(*10^6)	0.0001
10 HCT (%)	38.46±10.09	36.24±6.71	0.0001
11 LDLc (mg/dL)	104.04±38.49	122.25±48.14	0.0001
12 CHL (mg/dL)	194.24±55.79	218.93±63.54	0.0001
13 TG (mg/dL)	157.94±75.40	153.86±67.74	0.749
14 HDLc (mg/dL)	47.76±24.46	48.07± 18.09	0.514
15 Urea (mg/dL)	42.12±25.55	62.63±51.08	0.0001
16 CRT (mg/dL)	1.00±0.44	1.48±2.96	0.0001
17 PLR	14.08±18.16	23.94±30.51	0.0001
18 NLR	4.55±6.03	11.15±18.11	0.0001
19 LHR	2.35±1.02	2.69±1.09	0.0001

were determined according to maximum youden index. The ages of the patients were evaluated simultaneously.

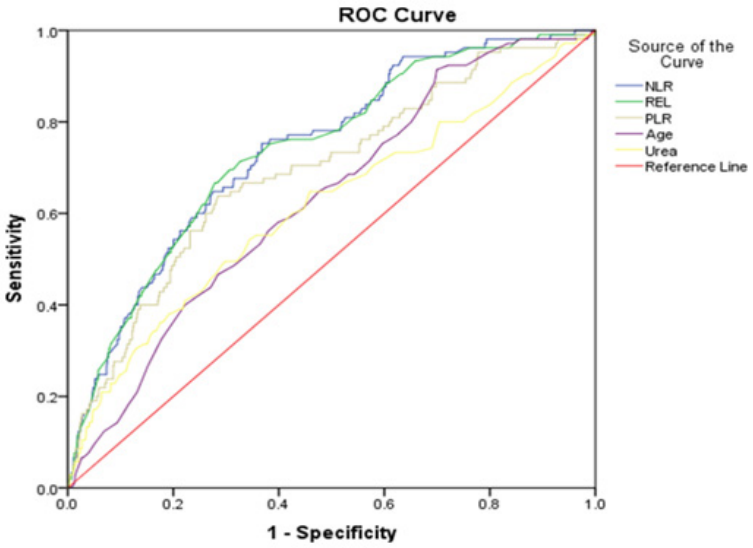

Figure 1. Receiver operating characteristics (ROC) curves for prediction of early mortality in male patients. REL; Reverse LYM (smaller LYM result indicates more early mortality)

RESULTS

Population characteristics and laboratory findings

The frequency of the early mortality in 1572 patients (743 male and 828 female) was 16% (n=252) who 105 were male and 147 were female. The mean ages of the patients were 73.8±12.03 years and 65.77±14.75 in patients with and without early mortality respectively that showed a significant difference (p = 0.001). No significant differences were observed between the mean ages of male and female with early mortality (72.87±1.21 years and 74.46±0.56 years respectively, p = 0.303). In male patients, LYM, WBCs, NET, HB, RBC, LDLc, CHL, HDLc, Urea, CRT, PLR, NLR level showed a significant difference between patients with and without early mortality (Table 1). The variable differences in female patients were presented in Table 2. In female patients, TG and HDLc level indicated no significant differences between patients with and without early mortality.

Odds ratios

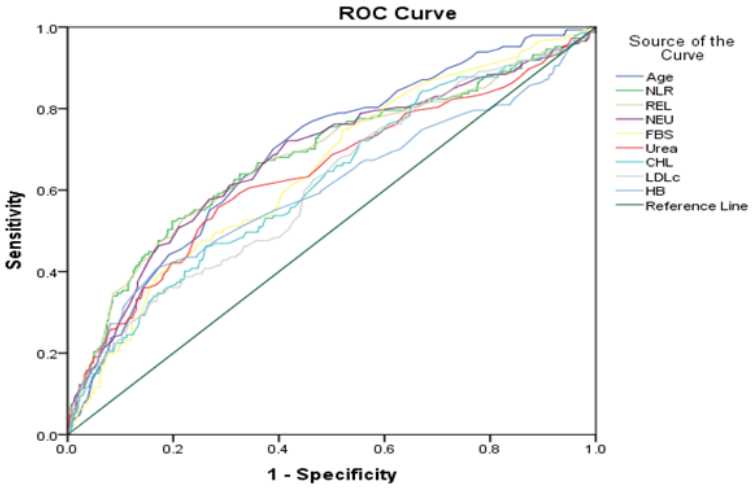

Figure 2. Receiver operating characteristics (ROC) curves for prediction of early mortality in female patient. REL; Reverse LYM (smaller LYM result indicates more early mortality).

Figure 1 and 2 depict the ROC curves of age and laboratory tests for the prediction of the early mortality in the male and female patients, respectively. AUC, cut-off points, sensitivity, specificity and odds ratios in cut-off points were indicatedin table 3. Among all investigated variables, NLR, LYM, PLR, Age and Urea levels have maximum AUC. Same analysis was performed for female patients and the results were summarized in Table 5. Table 4 and 6 showed the results of multivariate logistic regression analysis for male and female patients respectively .age and urea levels predict early mortality in both gender independently but LYM, FBS, CHL and HB have good predictive power only in female patients.

DISCUSSION

Several factors affect early or in hospital mortality after ischemic stroke including interval time between stroke and emergency measurements, quality health care and population characteristics (genetic, education, economic condition and etc).[13-15] Our results showed that the early mortality rates are higher in female than male patients. While other studies demonstrated that the incidence and prevalence of stroke are higher in male than female.[16] Moreover, the variables that predict early mortality are different between male and female. Age and urea level predicted mortality in both genders but HB, LYM and FBS predict early mortality only in male patients. These findings could be interpretedin two ways. First, discussion of etiologic roles of these variables in mortality rate increase .second, the importance of gender-dependent prediction pattern in clinical practices and settings.

In the present study, age is an independent predictor of early mortality and underlying mechanisms may include hypertension, diabetes, dyslipidemia and cardiovascular problems because these comorbidities are more frequent in older patients.[17] Our data analysis showed that there is a positive correlation between age and both systolic and diastolic blood pressures and the ages of the patients with diabetes are significantly higher than non-diabetic ones (data not shown).

Besides age, urea level is an independent predictor that could be useful in both genders. Previous studies showed that kidney function is a key factor in ischemic stroke etiology.[18-20] Bhatia et al reported higher BUN per CR ratio predicted poor outcome independently. Similar results observed by Firoozabadi et al in Iranian population.[21] The poor prognostic value of elevated serum urea was also confirmed by others.[22,23] Mathisen et al. showed that elevated serum creatinine is associated with higher long-term mortality rate.[24] In Walter et al study, serum urea to creatinine ratio was associated with higher mortality risk.[25] Literature reviews confirmed our results that urea may be a good candidate for prediction of early mortality in the clinical setting.

Our findings also showed that HB, LYM and FBS may be useful independent predictors in male but not female patients. Thus diabetic, anemic and lymphocytopenic male patients impose higher risk of early mortality. In these regards, Pulsinelli et al. study indicated that diabetes is an important risk factor for in hospital mortality and can be considered as a poor prognostic index for early mortality.[26] FBS could not predict early mortality in female that may be due to difference in prevalence and pathogenesis of diabetes between genders.[27]

In clinical setting, lower HB is an important biomarker in the diagnosis of anemia.[28] Other studies reported that anemia is a poor prognosis factor for ischemic stroke patients.[29] HB level

depends on several factors such as hormones and physical activity that may justify our results.

Our results showed that NLR has good predictive power but multivariate logistic regression analysis demonstrated that NLR is not an independent predictor. On the other hand lower LYM is associated with higher early mortality rate in male patients independently. Therefore, we conclude, the ROC analysis results about NLR is due to changes in LYM but not NET. The results of our study indicated that gender is an important factor in prediction of early mortality in ischemic stroke patients. The risk of early mortality is higher in older and hyperuremic patients. Ultimately, age and serum urea levels could be proposed as independent and common predictive variables for clinical setting in both genders.

Table 3. Early mortality prediction in male patients

		Male			
Variable	**AUC(CI)**	**Cut-off point**	**Sensitivity**	**Specificity**	**Odd ratio in cut-off point**
NLR	0.741 (0.693-0.788)	4.0278	0.752	0.632	5.22(CI: 3.306- 8.254)
LYM	0.739(0.691-0.788)	14.245	0.667	0.721	5.180(CI: 3.391-7.913)
PLR	0.692(0.638-0.747)	14.2672	0.638	0.715	4.427(CI: 2.920-6.712)
Age	0.631(0.579-0.683)	57.5	0.924	0.279	4.682(CI: 2.253-9.727)
Urea	0.614(0.553-0.675)	51.5	0.495	0.701	2.301(CI: 1.541-3.436)

AUC ROC: area under the receiver operating characteristic curve; NLR: neutrophil-to-lymphocyte ratio; LYM: lymphocytes; and PLR: platelet to lymphocyte ratio; The Odd ratio indicates the risk of early mortality.

Table 4: Independent predictors of early mortality by multivariate logistic regression analysis male patients

Variable	**Standard B value**	**P value**	**Odds ratios**
NLR	0.548	0.195	1.729 (CI: 0.755 – 3.964)
LYM	0.737	0.063	2.090 (CI: 0.961– 4.547)
PLR	0.475	0.132	1.609 (0.867 – 2.985)
Age	1.321	0.001	3.747 (1.780– 7.891)
Urea	0.484	0.024	1.622 (1.065 – 2.471)

Table 5. Early mortality prediction in female patients

		Female			
Test	**AUC(CI)**	**Cut-off point**	**Sensitivity**	**Specificity**	**Odd ratio in cut-off point**
Age	0.692(0.648-0.736)	68.5	0.769	0.463	3.862(CI: 2.594-5.749)
NLR	0.682(0.631-0.733)	3.8929	0.667	0.36	3.559(CI: 2.482-5.103)
LYM	0.679(0.628-0.731)	14.044	0.537	0.222	4.078(CI: 2.878-5.778)
NET	0.678(0.628-0.728)	71.8	0.721	0.416	3.636(CI: 2.496-5.297)
FBS	0.648(0.602-0.694)	162	0.429	0.204	2.294(CI: 2.056- 4.159)
Urea	0.641(0.589-0.693)	48.5	0.524	0.26	3.132(CI:2.217-4.425)
CHL	0.619(0.570-0.669)	163.5	0.844	0.673	2.625(CI: 1.659-4.155)
LDLc	0.613(0.564-0.662)	93.5	0.673	0.511	1.974(CI: 1.376-2.831)
HB	0.603(0.548-0.659)	11.148	0.408	0.169	3.394(CI: 2.372-4.856)

AUC ROC: area under the receiver operating characteristic curve; NLR: neutrophil-to-lymphocyte ratio; LYM: lymphocytes; PLR: platelet to lymphocyte ratio; FBS: Fasting blood sugar; CHL: cholesterol; LDLc: Low-density lipoprotein cholesterol; and HB hemoglobin. The Odd ratio indicates the risk of early mortality.

Table 6. Independent predictors of early mortality by multivariate logistic regression analysis male patient

Variable	**Standard B value**	**P value**	**Odds ratios**
Age	1.109	0.000	3.032 (CI: 1.974 – 4.658)
NLR	0.215	0.587	1.240 (CI: 0.571 – 2.691)
LYM	0.731	0.012	2.077 (CI 1.171 – 3.686)
NET	0.438	0.205	1.550 (CI: 0.787 – 3.051)
FBS	1.020	0.000	2.773 (CI: 1.879 – 4.092)
Urea	0.789	0.000	2.202 (CI: 1.505 – 3.221)
CHL	0.620	0.040	1.858 (CI: 1.029 – 3.356)
LDLc	0.372	0.126	1.451 (CI: 0.901 – 2.338)
HB	0.936	0.000	2.550 (CI 1.720 – 3.781)

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