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The strong predictive role and their day-dependent behavior of blood urea nitrogen and complete blood count in COVID-19's inpatients prognosis

Mohammad Fayaz [1], Vahid Tajari [2], Mohammad Hosein Taziki Balajelini [3], Abdolhalim Rajabi [4], Seyed Mehran Hosseini [5*]

1. Department of Biostatistics, Allameh Tabataba'i University, Tehran, Iran
2. Student Research Committee, Golestan University of Medical Sciences, Gorgan, Iran
3. Department of Surgery, School of Medicine, Golestan University of Medical Sciences, Gorgan, Golestan, Iran
4. Environmental Health Research Center, Faculty of Health, Golestan University of Medical Sciences, Gorgan, Iran
5. Department of Physiology, Neuroscience Research Center, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

* Correspondence: Seyed Mehran Hosseini. Department of Physiology, Neuroscience Research Center, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran. Tel: +989113736634; Email: hosseini@goums.ac.ir

Abstract

Background: The outcome of hospitalized COVID-19 patients is predictable according to demographic, clinical, laboratory, and imaging risk factors. We aimed to determine the best outcome predictors and their trends during 30 days of hospitalization.

Methods: This retrospective study was conducted on moderate to severe hospitalized COVID-19 patients from 26 January 2020 to 13 January 2021. The length of stay in the hospital was considered as the time interval between admission and discharge, and the patient's final condition was defined as either dead or alive. Demographic, clinical, and laboratory data were collected from the hospital information system. The generalized additive model and the Cox regression model were used to model data.

Results: Of the 1520 hospitalized COVID-19 patients, 232 (15.26%) died and 1288 survived or reached the end of 30 days of hospitalization. We selected demographic, clinical, and 131 independent laboratory variables. Blood urea nitrogen (BUN) had a nearly double average in the dead group (44.603 [± 25.408] mg/dL) than the survived group (21.304 [± 13.318] mg/dL), and the lymphocyte (Lymph) count showed the opposite trend. The estimated hazard ratio (HR) of these 2 factors was higher than 1 and was statistically significant. In daily stay trends, the hazard function of them also increased rapidly after 15 days.

Conclusion: Blood urea nitrogen and complete blood count provide strong predictive clues about the prognosis of hospitalized COVID-19 patients, and rapid dynamic changes in the second week can predict a poor outcome in these patients.

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Introduction

The final outcome of hospitalized cases of COVID-19 may be catastrophic and is influenced by several factors, including the actual potential of health systems and the capacity of intensive care units (ICUs) (1,2).

In COVID-19, some prognostic factors are related to the patient, while others are related to the SARS-CoV-2 virus. Patient-related factors include gender, age, underlying disease, and immune status. Virus-related factors include virus variants, the initial number of viruses entering the patient's body, and the route that they enter (3-9). In severe cases, hospitalization is mandatory. The duration of hospitalization of patients is different, and its range is very wide in survived and dead cases (10-12). Predicting the severity and the course of the disease during hospitalization is very important. These predictions are usually provided based on demographic, clinical, radiological, and laboratory data. There are many reports on the role of each of these factors or a combination of them in the prognosis of hospitalized COVID-19 patients (13-17). The findings of these studies were based on the patients' tests at admission, the patients' condition during the hospitalization, or the patients' information at discharge (18-23). However, most studies focused on the initial conditions of cases at admission, and the number of studies that provided statistically verified models for their data is limited (24,25). In our study, the predictive effect of demographic factors and changes in laboratory tests on the final outcome of hospitalized COVID-19 patients was studied. Indeed, the aim was to explore the best deterministic dynamic changes and the time of their occurrences during the hospitalization period that had the most predictive value for the 1-month prognosis after hospitalization of COVID-19 patients.

Methods

A total of 1982 COVID-19 patients were enrolled in this retrospective study. They were admitted to a referral university hospital in Gorgan, Iran, from 26 January 2020 to 13 January 2021. Diagnosis of COVID-19 was based on a positive SARS-CoV-2 real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test (26).

Demographic, clinical, and laboratory variables were collected from the hospital information system, a formal digital registry system. For all the studied cases, the length of stay in the hospital was considered as the time interval between admission and discharge, and the patient's final condition was defined as either dead or alive. Among different variables related to the patients in the hospital, we collected demographic, clinical, and laboratory variables. The most related variables were 131 independent laboratory tests that had been measured and recorded at different hours and on different days of hospitalization from each patient. Therefore, the dataset was collected and cleaned according to considering less than 6% missing value for each variable. Thereafter, only 17 independent laboratory parameters still existed. They were white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), hematocrit, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelet (Plt), neutrophil (Neut), eosinophil (Eos), lymphocyte (Lymph), monocyte (Mono), blood urea nitrogen (BUN), creatinine (Cr), sodium ion (Na^+), potassium ion (K^+), and gender. The only exclusion criterion was "more than 30 days of hospitalization." Finally, only 1520 patients remained, of whom 232 died and 1288 survived or reached the end of 30 days. The last groups (eg, "not death and stay in the hospital after the 30 days") were considered the right censor. The hourly observation records were not regularly observed in each hour, varied from one patient to another patient, and were sparse; therefore, we introduced 2 new indices as follows: Data preparation step 1 was averaging of all hourly measurements for each index during the hospitalization of each patient, called "total average of the index," $\{\bar{X}_i = \sum_j^{m_i} \frac{X_{ij}}{m_i}, \{i: 1, \dots, n\}, \{j: 1, \dots, m_i\}\}$, where i was an index for the laboratory variables from 1 to 16, and j was an index for each measurement of the index from 1 to m_i. In some analysis, we also made a daily average of each index of each patient based on the hourly observations in each day, called the "daily average of the index, " $\{\bar{X}_i(t) = \sum_j^{m_{it}} \frac{X_{ij}}{m_{it}}, \{i: 1, \dots, n\}, \{j: 1, \dots, m_{it}\}, \{t: 1, \dots, T_i\}\}$, where i was an index for the laboratory variables from 1 to $n = 16$, j was an index for each measurement of the index from 1 to m_{it}, t was an index for hospital stay days from 1 to at most $T_i = 30$, and m_{it} was the total measurements for laboratory variable i and the day of stay t. The $\bar{X}_i$ and $\bar{X}_i(t)$ were calculated for each patient. All data management and statistical analyses were performed using R version 4.0.2 and R Studio version 1.3.959 (27)

Statistical methods

The descriptive statistics of demographic and clinical variables were reported as a percentage for categorical one and mean and SD for continuous one grouped by total, survived, and dead cases, respectively. The P value for testing the differences between survived and dead cases was reported with a chi-square test for categorical data and a t test or Mann-Whitney test for continuous tests. The correlation between laboratory covariates was also reported using the Pearson correlation coefficient.

The length of stay in the hospital from beginning to *"at most after 30 days"* was recorded for each patient with 3 statuses, including death, survived, or right censored (not death and stay in the hospital after the 30 days). Therefore, the Cox

regression model was used to model the length of stay with censors and demographic and laboratory covariates. In this regard, the univariate Cox regression was fitted to each covariate separately (model 1), the multivariate Cox regression with all covariates was considered (model 2), and then the backward variable selection was used in the previous model based on the Akaike information criterion (AIC; model 3): $AIC = 2k - 2\ln(\hat{L})$, number of parameters k and estimated likelihood function $\hat{L}$ (28). Finally, we plotted the estimated hazard ratio (HR) with its 95% CI of model 3 with the forest plot (29). We also studied and selected the variables with the LASSO (Least Absolute Shrinkage and Selection Operator) method and 10-fold cross-validation (30). The daily pattern of some single-selected variables was modeled with the frailty model (31). We also computed the time-dependent area under the curve (AUC) and integrated AUC (IAUC) for each model with the Song and Zhou estimator; in this regard, we split data into the training (80%) and test (20%) datasets. Also, we estimated the model in the training dataset and got the result with the test dataset (32,33).

The generalized additive model (GAM) with the logit link function, binary response (dead and survived/still alive), and varying coefficient model were used (34,35). The covariates in the previous Cox regression models were averaged over all measurements during the length of stay in the hospital for each patient, and the averages were entered into the model. However, in the GAM, we entered the daily average of the covariates with the cubic regression spline. In this regard, 2 strategies were considered: First, the univariate GAM with only 1 daily average covariate was considered in the spline basis (A). Second, the multivariate GAM with all covariates was considered a total average, except for 1 covariate with a spline term on the daily average (B). Strategy A estimates the trends of the staying days concerning the daily average covariate within 30 days in the GAM model, and strategy B estimates the trends of the staying days for the daily average covariate adjusted by other total average covariates.

Results

According to Table 1, of the 1520 cases, 232 (15.26%) died, and all laboratory variables were significant between the survived and dead cases ($P < 0.05$). Among them, WBC, MCV, Neut, BUN, Cr, Na+, and K+ had greater averages in the dead group than in the survived group. Blood urea nitrogen had a nearly double average in the dead group (44.603 ± 25.408 mg/dL) than in the survived group (21.304 ± 13.318 mg/dL); however, the Lymph count showed the opposite trend, with an average of 10.428% ± 5.524% in the dead group and 18.311% ± 8.466% in the survived group. The Pearson correlation coefficient between laboratory variables was plotted with the heat map (Figure 1-1 in the supplementary file), showing that some of them have a strong correlation (ie, HCT, HGB, and RBC).

Table 1. The descriptive statistics of the demographic and clinical characteristics

Group	Variable	Unit	Total(n=1520)	Survived(n=1288)	Dead(n=232)	P value
Demographic	Gender	-	724 (Female, 47.6%)	622 (Female, 48%)	102 (Female, 44%)	0.253
Laboratory	WBC	(X103/µL)	8.746 ± 3.54	8.133 ± 3.164	12.148 ± 3.59	<0.05
	RBC	(X106/µL)	4.327 ± 0.677	4.364 ± 0.653	4.121 ± 0.766	<0.05
	HGB	(g/dL)	12.402 ± 1.836	12.517 ± 1.77	11.767 ± 2.054	<0.05
		(%)	37.92 ± 4.958	38.145 ± 4.753	36.673 ± 5.825	<0.05
	MCV	(fl)	88.387 ± 7.924	88.125 ± 7.899	89.84 ± 7.923	<0.05
	MCH	(pg)	28.892 ± 3.118	28.911 ± 3.145	28.783 ± 2.966	<0.05
	MCHC	(%)	32.662 ± 1.572	32.776 ± 1.561	32.032 ± 1.483	<0.05
	Plt	(X103/µL)	234.993 ± 78.243	239.717 ± 78.921	208.766 ± 68.846	<0.05
	Neut	(%)	78.272 ± 8.539	77.103 ± 8.447	84.763 ± 5.655	<0.05
	Eos	(%)	1.969 ± 0.815	2.026 ± 0.836	1.648 ± 0.597	<0.05
	Lymph	(%)	17.108 ± 8.568	18.311 ± 8.466	10.428 ± 5.524	<0.05
	Mono	(%)	1.857 ± 0.548	1.9 ± 0.556	1.617 ± 0.431	<0.05
	BUN	(mg/dl)	24.86 ± 17.852	21.304 ± 13.318	44.603 ± 25.408	<0.05
	Cr	(mg/dl)	1.33 ± 0.972	1.236 ± 0.853	1.853 ± 1.355	<0.05
	Na	(mEq/L)	140.413 ± 4.144	140.214 ± 3.801	141.518 ± 5.567	<0.05
	K	(mEq/L)	4.173 ± 0.463	4.134 ± 0.422	4.389 ± 0.602	<0.05

Mean + (SD) or % n. P values were calculated by the t test, Mann-Whitney test, and χ^2 test.
Abbreviations: WBC, White Blood Cell; RBC, Red Blood Cell; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean Cell Volume; MCH, Mean Cell Hemoglobin; MCHC, Mean Cell Hemoglobin Concentration; Plt, Platelet; Neut, Neutrophil; Eos, Eosinophil; Lymph, Lymphocyte; Mono, Monocyte; BUN, Blood Urea Nitrogen; Cr, Creatinine; Na+, Sodium ion; K+, Potassium ion.

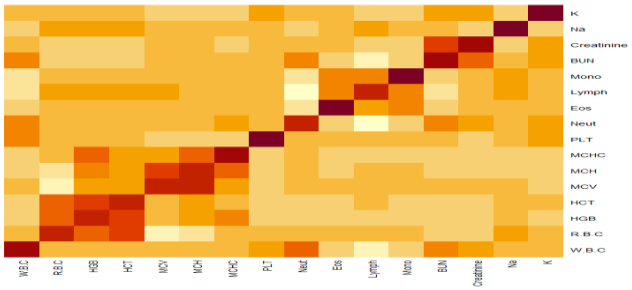

Figure 1-1- The heat map of the Pearson correlation coefficient between clinical variables. The higher value has red colors and the lower values have yellow colors.

Based on Table 1-1, in model 1 or univariate Cox regressions, the calculated Hazard Ratios (HR) for K (2.31), Cr (1.424), WBC (1.177), Neut (1.102), Na (1.061), and BUN (1.03) were above 1 and showed statistical significance at 5% type I error level. In model 2 (the multivariate Cox regression), only MCH (3.363), WBC (1.069), and BUN (1.017) had estimated HR higher than 1 and were statistically significant (Table 1-1). The comparison between models 1 and 2 according to the IAUC and time-dependent AUC is illustrated in Figure 1. Both models exhibited similar performance based on the Area Under the Curve (AUC) metric, showcasing a declining trend over time with AUC values ranging between 0.68 and 0.75, indicating a high level of accuracy. Models 2 and 3 are the same; therefore, model 3 was not plotted in this figure. According to Figure 3, the estimated HRs in model 3 were all significant at 5%, except for Na^+ ($P = 0.066$), but it remained in the model. The adjusted estimated HR for MCH was the highest among others and was 3.13 (1.06-9.23). On the other hand, WBC, MCHC, BUN, and Na^+ covariates had non-zero coefficients in the LASSO Cox regression (10-fold cross-validation) with the lowest C-index (Table 1-2 and Figure 1-2).

Table 1-1. The ANOVA table of Cox regression models group by model strategy including univariate (1), multivariate (2), and AIC selection (3).

Model strategy	Variables	COEF	HR	95% CI		P-Value
				Lower	Upper	
1	Gender	0.087	1.09	0.841	1.414	0.51
2		-0.153	0.858	0.648	1.138	0.288
3		-	-	-	-	-
1	WBC	0.163	1.177	1.138	1.218	0
2		0.067	1.069	1.006	1.137	0.032*
3		0.095	1.100	1.056	1.146	0.000*
1	RBC	-0.156	0.856	0.703	1.041	0.12
2		-0.382	0.682	0.212	2.193	0.521
3		-	-	-	-	-
1	HGB	-0.093	0.912	0.847	0.981	0.01*
2		-0.065	0.937	0.174	5.056	0.940
3		-	-	-	-	-
1	HCT	-0.013	0.987	0.961	1.013	0.32
2		0.102	1.107	0.628	1.951	0.725
3		0.031	1.031	1.005	1.058	0.019*
1	MCV	0.015	1.015	0.997	1.034	0.11
2		-0.385	0.681	0.466	0.995	0.047*
3		-0.342	0.710	0.507	0.995	0.047*
1	MCH	-0.027	0.973	0.93	1.018	0.23
2		1.213	3.363	1.066	10.608	0.039*
3		1.140	3.128	1.061	9.226	0.039*
1	MCHC	-0.24	0.787	0.722	0.857	<0.05*
2		-1.244	0.288	0.081	1.029	0.055
3		-1.216	0.296	0.113	0.776	0.013*
1	PLT	-0.004	0.996	0.995	0.998	<0.05*
2		-0.001	0.999	0.997	1.001	0.237
3		-	-	-	-	-
1	Neut	0.097	1.102	1.07	1.134	<0.05*
2		-0.212	0.809	0.603	1.087	0.160
3		-	-	-	-	-
1	Eos	-0.728	0.483	0.359	0.65	<0.05*
2		-0.292	0.747	0.524	1.064	0.106
3		-	-	-	-	-
1	Lymph	-0.102	0.903	0.877	0.929	<0.05*
2		-0.236	0.790	0.590	1.057	0.113
3		-0.031	0.970	0.941	1.000	0.048*
1	Mono	-0.794	0.452	0.322	0.635	<0.05*
2		-0.166	0.847	0.539	1.333	0.474
3		-	-	-	-	-
1	BUN	0.03	1.03	1.025	1.035	<0.05*
2		0.017	1.017	1.009	1.026	<0.000*
3		0.023	1.023	1.018	1.029	<0.000*
1	Creatinine	0.353	1.424	1.323	1.532	<0.05*
2		0.091	1.096	0.957	1.254	0.187
3		-	-	-	-	-
1	Na	0.059	1.061	1.035	1.086	<0.05*
2		0.027	1.027	0.998	1.058	0.068
3		0.026	1.026	0.998	1.055	0.066
1	K	0.837	2.31	1.846	2.891	<0.05*
2		0.148	1.159	0.854	1.574	0.344
3		-	-	-	-	-

Models: Model 1 is univariate model for each covariate, model 2 is a multivariate model for all covariates, and model 3 is an AIC based selection model of model 2.

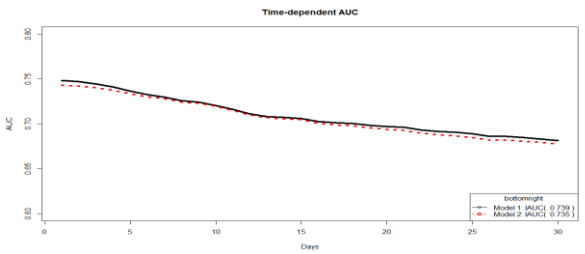

Figure 1. The time-dependent area under the curve for models 1 and 2 with the integrated area under the curve index
Abbreviation: AUC, Area under the curve.

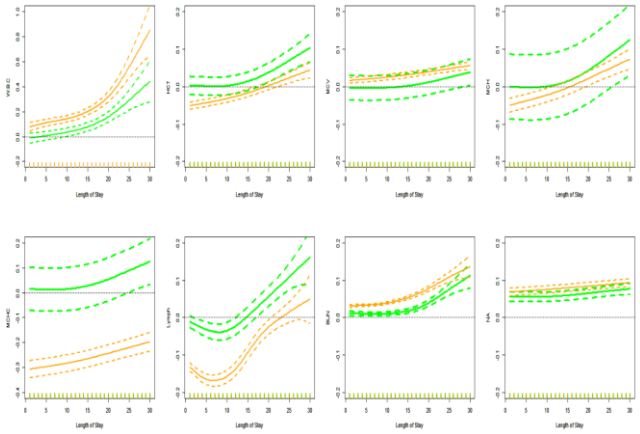

Figure 3. The estimated spline of the generalized additive model with logistic link function and binomial family in 2 scenarios: 1) Univariate: considering only 1 covariate (Orange); 2) Multivariate: considering multiple covariates (Green). The models are from Table 1-3.
Abbreviations: WBC, White Blood Cell; MCHC, Mean Cell Hemoglobin Concentration.

Table 1-2. The estimated covariates of Cox regression in minimum λ and within one standard error

Models		Within one Se	Minimum
Lambda	λ	0.05801639	0.02756
	log (λ)	-2.84703	-3.59139
Covariates	Gender	.	.
	WBC	0.024	0.068
	RBC	.	.
	HGB	.	.
	HCT	.	.
	MCV	.	.
	MCH	.	.
	MCHC	.	-0.051
	PLT	.	.
	Neut	.	.
	Eos	.	.
	Lymph	.	.
	Mono	.	.
	BUN	0.018	0.021
	Creatinine	.	.
	Na	.	0.006
	K	.	.

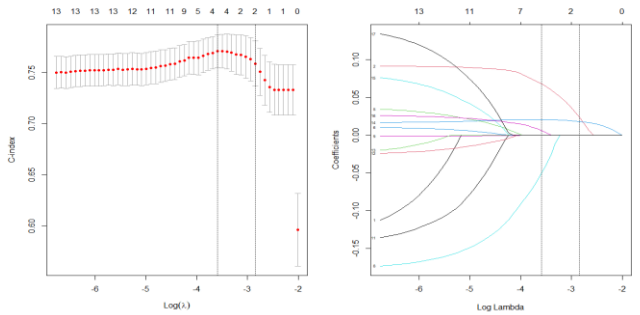

Figure 1-2- The regularization paths for Cox regression with LASSO setting. The vertical dotted lines are boundaries of minimum lambda and within one standard error. (right). The 10-fold cross-validation results against C-index and log (λ) (left)

The daily stay trends of the discussed variables (WBC and BUN) were estimated and plotted in Figure 1-3, showing that the hazard function increases rapidly after 15 days.

While gender did not prove to be significant in Model 3, numerous studies have highlighted the impact of demographic factors such as gender on blood-related measurements (6,8,9,34,36,37). Therefore, further analyses were repeated for each gender separately in supplementary 2 (Table 2-1: the univariate Cox regression by gender; Table 2-2: the multivariate Cox regression by gender). It showed that different variables remained in model 3, but three of them (ie, WBC [HR > 1], MCHC, and Lymph [HR < 1]) were in both models for males and females (Table 2-3, Figure 2-1, Figure 2-2, Figure 2-3, and Table 2-4).

GAM Model: The estimated splines of the GAM are presented in Figure 2 for both (A) Univariate in orange and (B) multivariate in green settings. The change of the estimated splines of stay days concerning WBC and BUN from 1 to 15 days was slow but, from 15 to 30, was very rapid and rapid, respectively; in addition, the behavior of A and B was almost the same. The Lymph had a different pattern; it decreased then increased rapidly from day 5 to 10. MCHC, HCT, MCV, and MCH had a monotonic increase, but Na+ had the same estimates on all days. Table 1-3 shows the estimated coefficients and their P values.

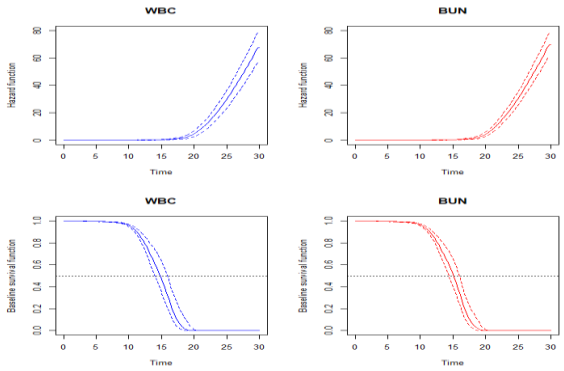

Figure 1-3- The hazard and survival functions for univariate frailty models colors. The left panel is for WBC and the right panel is for BUN. The estimated and 95% confidence interval of HR for WBC and BUN are 1.07 (1.06-1.09) and 1.01 (1.01-1.02), respectively. The p-values are <0.05 and <0.05.

Table 2-1. The estimated coefficients for Univariate Cox Regression group by Gender

Gender	Covariates	Coefficients	HR	P-Value
Female	WBC	0.163	1.177	0.00*
Male	WBC	0.167	1.182	0.00*
Female	RBC	-0.072	0.93	0.65
Male	RBC	-0.261	0.77	0.05*
Female	HGB	-0.129	0.879	0.05*
Male	HGB	-0.098	0.906	0.04*
Female	HCT	-0.019	0.981	0.41
Male	HCT	-0.017	0.983	0.33
Female	MCV	-0.007	0.993	0.57
Male	MCV	0.037	1.037	0.01*
Female	MCH	-0.068	0.935	0.03*
Male	MCH	0.011	1.011	0.74
Female	MCHC	-0.302	0.739	0.00*
Male	MCHC	-0.212	0.809	0.00*
Female	PLT	-0.003	0.997	0.03*
Male	PLT	-0.004	0.996	0.00*
Female	Neut	0.09	1.094	0.00*
Male	Neut	0.103	1.109	0.00*
Female	Eos	-0.408	0.665	0.05
Male	Eos	-1.047	0.351	0.00*
Female	Lymph	-0.098	0.907	0.00*
Male	Lymph	-0.108	0.898	0.00*
Female	Mono	-0.735	0.479	0.01*
Male	Mono	-0.846	0.429	0.00*
Female	BUN	0.029	1.029	0.00*
Male	BUN	0.03	1.031	0.00*
Female	Creatinine	0.377	1.458	0.00*
Male	Creatinine	0.336	1.399	0.00*
Female	Na	0.041	1.042	0.01*
Male	Na	0.093	1.098	0.00*
Female	K	0.967	2.63	0.00*
Male	K	0.768	2.155	0.00*

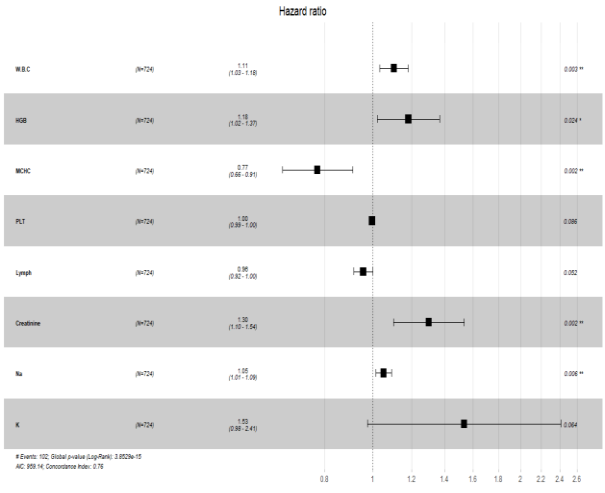

Figure 2-1. The forest plot for multivariate Cox regression based on the AIC for females.

Table 2-2. The estimated Multivariate Cox Regression group by Gender

Gender	Covariates	Coefficients	HR	P-Value	95% CI	
					Lower	Upper
Female	WBC	0.078	1.081	0.108	0.983	1.189
Male	WBC	0.071	1.074	0.087	0.990	1.165
Female	RBC	-0.872	0.418	0.450	0.044	4.012
Male	RBC	0.212	1.236	0.851	0.135	11.280
Female	HGB	0.446	1.562	0.768	0.080	30.429
Male	HGB	-0.185	0.831	0.872	0.088	7.868
Female	HCT	0.006	1.006	0.990	0.382	2.651
Male	HCT	0.073	1.076	0.861	0.475	2.436
Female	MCV	-0.051	0.950	0.876	0.498	1.812
Male	MCV	-0.607	0.545	0.039*	0.306	0.970
Female	MCH	0.021	1.021	0.983	0.144	7.230
Male	MCH	2.060	7.848	0.015*	1.504	40.944
Female	MCHC	-0.397	0.672	0.708	0.084	5.386
Male	MCHC	-1.922	0.146	0.039	0.024	0.906
Female	PLT	-0.002	0.998	0.119	0.995	1.001
Male	PLT	0.000	1.000	0.933	0.997	1.003
Female	Neut	-0.134	0.875	0.550	0.564	1.356
Male	Neut	-0.301	0.740	0.144	0.494	1.108
Female	Eos	0.137	1.147	0.602	0.685	1.919
Male	Eos	-0.672	0.511	0.010*	0.306	0.853
Female	Lymph	-0.171	0.842	0.435	0.548	1.296
Male	Lymph	-0.315	0.730	0.124	0.489	1.091
Female	Mono	-0.386	0.680	0.307	0.324	1.425
Male	Mono	-0.061	0.941	0.832	0.534	1.656
Female	BUN	0.005	1.005	0.504	0.990	1.020
Male	BUN	0.027	1.027	0.000*	1.016	1.039
Female	Creatinine	0.200	1.221	0.093	0.967	1.541
Male	Creatinine	0.021	1.021	0.822	0.850	1.228
Female	Na	0.045	1.046	0.031*	1.004	1.089
Male	Na	0.009	1.009	0.690	0.966	1.054
Female	K	0.382	1.466	0.119	0.906	2.371
Male	K	-0.062	0.940	0.771	0.621	1.423

Table 2-3. The estimated multivariate Cox Regression with backward selection based on AIC group by Gender

Gender	Covariates	Coefficients	HR	P-Value	95% CI	
					Lower	Upper
Female	WBC	0.100	1.105	0.003	1.034	1.181
	MCHC	-0.258	0.773	0.002	0.656	0.910
	Lymph	-0.044	0.957	0.052	0.916	1.000
	HGB	0.168	1.182	0.024	1.023	1.367
	PLT	-0.002	0.998	0.086	0.995	1.000
	Creatinine	0.263	1.301	0.002	1.103	1.535
	Na	0.051	1.052	0.006	1.015	1.092
	K	0.428	1.534	0.064	0.976	2.411
Male	WBC	0.073	1.075	0.044	1.002	1.154
	MCHC	-1.966	0.140	0.002	0.040	0.488
	Lymph	-0.297	0.743	0.079	0.533	1.035
	RBC	0.328	1.388	0.036	1.021	1.886
	MCV	-0.593	0.553	0.009	0.354	0.863
	MCH	2.034	7.648	0.005	1.869	31.304
	Neut	-0.284	0.753	0.094	0.541	1.049
	Eos	-0.697	0.498	0.007	0.300	0.826
	BUN	0.027	1.028	0.000	1.021	1.035

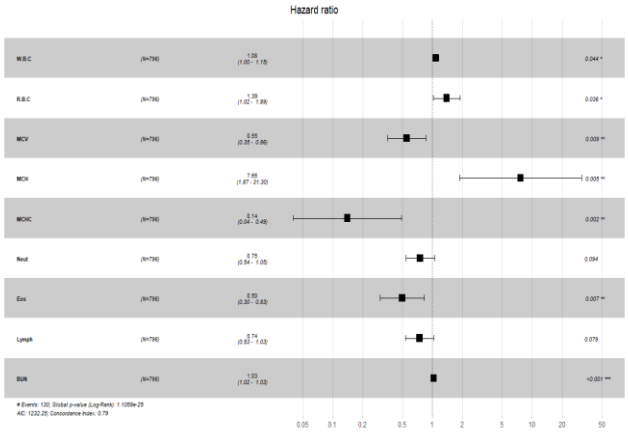

Figure 2-2. The forest plot for multivariate Cox regression based on the AIC for males.

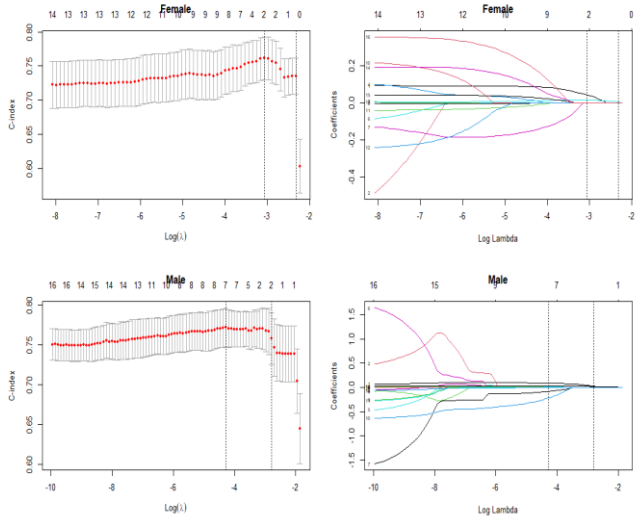

Figure 2-3. The regularization paths for Cox regression with LASSO setting group by gender. The vertical dotted lines are boundaries of minimum lambda and within one standard error. (right). The 10-fold cross-validation results against C-index and log (λ) (left). The female is in the first row and the male is in the second row.

Table 2-4. The estimated coefficients of Cox regression in minimum λ and within one standard error group by Gender

Gender		**Female**		**Male**	
Models		**Within one Se**	**Minimum**	**Within one Se**	**Minimum**
Lambda	**λ**	0.098	0.046	0.061	0.013
	log (λ)	-2.316	-3.060	-2.796	-4.284
Covariates	**WBC**	.	0.043	0.024	0.089
	RBC	.	.	.	.
	HGB	.	.	.	.
	HCT	.	.	.	0.012
	MCV	.	.	.	0.015
	MCH	.	.	.	.
	MCHC	.	.	.	-0.083
	PLT	.	.	.	.
	Neut	.	.	.	.
	Eos	.	.	.	-0.217
	Lymph	.	.	.	.
	Mono	.	.	.	.
	BUN	0.003	0.015	0.020	0.024
	Creatinine	.	.	.	.
	Na	.	.	.	0.005
	K	.	.	.	.

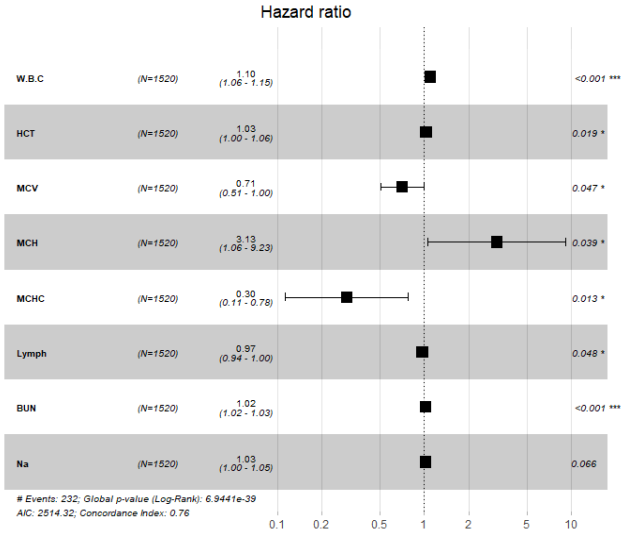

Figure 2. The forest plot of model 3.
The significance level is *0.5, **0.01, and ***0.001.
Abbreviations: WBC, White Blood Cell; RBC, Red Blood Cell; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean Cell Volume; MCH, Mean Cell Hemoglobin; MCHC, Mean Cell Hemoglobin Concentration; Lymph, Lymphocyte; BUN, Blood Urea Nitrogen; Na+, Sodium ion.

Table 1-3. The comparison between 8 models with considering generalized additive model with logistic link function and binomial family group by (A) Univariate and (B) Multivariate

Covariates	Indices	Models															
		1		2		3		4		5		6		7		8	
	# Covariates	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Intercept	Estimate	-2.76	35.215	0.30	0.685	-3.07	19.770	-0.19	19.145	8.30	9.058	0.54	-50.096	-2.29	-17.117	-11.29	17.576
	SE	0.08	14.221	0.17	13.361	0.32	10.387	0.26	10.302	0.54	8.119	0.06	12.252	0.05	14.171	0.70	14.310
	P-Value	<0.05	0.013	0.08	0.959	<0.05	0.057	0.45	0.063	<0.05	0.265	<0.05	0.000	<0.05	0.227	<0.05	0.219
WBC	Estimate	*	*	-	0.141	-	0.143	-	0.143	-	0.140	-	0.206	-	0.168	-	0.136
	SE	*	*	-	0.017	-	0.017	-	0.017	-	0.017	-	0.012	-	0.017	-	0.016
	P-Value	<0.000	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000
RBC	Estimate	-	-0.615	-	-0.544	-	-0.790	-	-0.713	-	-0.662	-	-0.649	-	-0.469	-	-0.642
	SE	-	0.240	-	0.219	-	0.245	-	0.242	-	0.230	-	0.226	-	0.235	-	0.227
	P-Value	-	0.010	-	0.013	-	0.001	-	0.003	-	0.004	-	0.004	-	0.045	-	0.005
HGB	Estimate	-	-0.591	-	0.096	-	-0.576	-	-0.574	-	-0.381	-	-0.695	-	-0.355	-	0.318
	SE	-	0.492	-	0.086	-	0.482	-	0.482	-	0.410	-	0.484	-	0.464	-	0.459
	P-Value	-	0.230	-	0.262	-	0.232	-	0.234	-	0.354	-	0.151	-	0.444	-	0.488
HCT	Estimate	-	0.234	*	*	-	0.259	-	0.249	-	0.180	-	0.277	-	0.133	-	-0.045
	SE	-	0.163	*	*	-	0.160	-	0.160	-	0.139	-	0.160	-	0.153	-	0.152
	P-Value	-	0.150	<0.000	<0.000	-	0.106	-	0.119	-	0.195	-	0.083	-	0.387	-	0.767
MCV	Estimate	-	0.282	-	0.302	*	*	-	0.010	-	0.156	-	0.323	-	0.379	-	0.352
	SE	-	0.119	-	0.116	*	*	-	0.020	-	0.059	-	0.115	-	0.111	-	0.113
	P-Value	-	0.018	-	0.009	<0.000	<0.000	-	0.609	-	0.008	-	0.005	-	0.001	-	0.002
MCH	Estimate	-	-0.845	-	-0.892	-	0.027	*	*	-	-0.451	-	-0.977	-	-1.143	-	-1.053
	SE	-	0.367	-	0.358	-	0.068	*	*	-	0.178	-	0.354	-	0.341	-	0.348
	P-Value	-	0.021	-	0.013	-	0.691	<0.000	<0.000	-	0.011	-	0.006	-	0.001	-	0.002
MCHC	Estimate	-	0.476	-	0.238	-	-0.325	-	-0.305	*	*	-	0.612	-	0.677	-	0.297
	SE	-	0.380	-	0.324	-	0.194	-	0.185	*	*	-	0.370	-	0.355	-	0.365
	P-Value	-	0.211	-	0.461	-	0.093	-	0.100	<0.000	<0.000	-	0.098	-	0.056	-	0.416
PLT	Estimate	-	-0.007	-	-0.007	-	-0.007	-	-0.007	-	-0.007	-	-0.008	-	-0.008	-	-0.008
	SE	-	0.001	-	0.001	-	0.001	-	0.001	-	0.001	-	0.001	-	0.001	-	0.001
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000
Neut	Estimate	-	-0.675	-	-0.266	-	-0.276	-	-0.280	-	-0.281	-	0.133	-	-0.264	-	-0.369
	SE	-	0.066	-	0.080	-	0.080	-	0.079	-	0.080	-	0.013	-	0.079	-	0.078
	P-Value	-	<0.000	-	0.001	-	0.001	-	0.000	-	<0.000	-	<0.000	-	0.001	-	<0.000
Eos	Estimate	-	-0.584	-	-0.280	-	-0.255	-	-0.262	-	-0.263	-	0.033	-	-0.323	-	-0.445
	SE	-	0.093	-	0.099	-	0.098	-	0.098	-	0.098	-	0.083	-	0.092	-	0.091
	P-Value	-	<0.000	-	0.005	-	0.010	-	0.008	-	0.008	-	0.692	-	<0.000	-	<0.000
Lymph	Estimate	-	-0.804	-	-0.404	-	-0.412	-	-0.416	-	-0.418	*	*	-	-0.414	-	-0.480
	SE	-	0.064	-	0.079	-	0.078	-	0.078	-	0.079	*	*	-	0.078	-	0.077
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	<0.000	<0.000	-	<0.000	-	<0.000
Mono	Estimate	-	-1.618	-	-1.027	-	-0.999	-	-1.007	-	-1.028	-	-0.648	-	-0.970	-	-1.054
	SE	-	0.126	-	0.133	-	0.131	-	0.131	-	0.132	-	0.105	-	0.126	-	0.125
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000
BUN	Estimate	-	0.041	-	0.037	-	0.037	-	0.038	-	0.037	-	0.037	*	*	-	0.043
	SE	-	0.003	-	0.003	-	0.003	-	0.003	-	0.003	-	0.003	*	*	-	0.003
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	<0.000	<0.000	-	<0.000
Creatinine	Estimate	-	-0.456	-	-0.415	-	-0.400	-	-0.402	-	-0.407	-	-0.407	-	-0.153	-	-0.493
	SE	-	0.056	-	0.054	-	0.054	-	0.054	-	0.054	-	0.054	-	0.043	-	0.049
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000
Na	Estimate	-	0.115	-	0.122	-	0.122	-	0.123	-	0.123	-	0.119	-	0.146	*	*
	SE	-	0.010	-	0.010	-	0.010	-	0.010	-	0.010	-	0.010	-	0.010	*	*
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	<0.000	<0.000
K	Estimate	-	0.552	-	0.427	-	0.451	-	0.446	-	0.446	-	0.402	-	0.739	-	0.438
	SE	-	0.100	-	0.098	-	0.097	-	0.097	-	0.097	-	0.096	-	0.093	-	0.094
	P-Value	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000	-	<0.000

Models: Considering splines in the model (1): **WBC**, model (2): **HCT**, model (3): **MCV**, model (4): **MCH**, model (5): **MCHC**, model (6): **Lymph**, model (7): **BUN**, model (8): **Na** group by **(A)** Univariate and **(B)** Multivariate. *Daily trend with multiplied/respect to that variable.

Discussion

In addition to the previous result, the result of univariate frailty models showed the important role of complete blood cell count (CBC) and BUN in determining the prognosis of hospitalized COVID-19 patients. These data may be clinically useful. Both tests are routine and simple and almost always available. These data are especially important for patients with a hospital stay of more than 2 weeks.

In COVID-19, there is a relatively high risk of kidney involvement and acute renal failure because there are large amounts of ACE2 protein on the surface of renal epithelial cells. This protein acts as the SARS-CoV-2 receptor, and its expression in the kidney has been reported to be more than 100 times that of lung tissue (38-40). Markers of renal function are regularly reported to have a strong association with the deterioration or death in COVID-19 patients. In the study by Ok et al, 139 patients were studied. BUN/Cr and neutrophil-to-lymphocyte ratios (NLRs) at admission were reported as 2 independent predictors of disease severity and death (41). In the study by Cheng et al, 305 patients were examined. In this study, the level of BUN and D dimer at admission had a strong relationship with the mortality rate of patients. In Cox regression analysis, the role of these 2 factors as 2 independent factors in determining the prognosis was identified. In other words, even after adjustment for the effect of age, sex, underlying disease, neutrophilia, lymphocytopenia, thrombocytopenia, albumin, lactate dehydrogenase, procalcitonin, and interleukin 6 (IL-6), the 2 factors were strongly associated with COVID-19 mortality (42). The importance of BUN as an independent factor in predicting patient mortality and also as a marker of disease severity has previously been reported in different diseases (43). In a study of 4176 ICU patients, the level of BUN at admission was associated with patient mortality. This finding was still present even after correcting the BUN value based on other confounding variables, including the extent of renal failure (44). In fact, the relationship between BUN (as an independent factor but unrelated to kidney function) and prognosis has been reported in various diseases. This relationship has been reported in all 3 timing states: the level at the beginning of hospitalization, the increasing trend during hospitalization, and the level of BUN at the end of hospitalization or discharge. The association of increased BUN with mortality has been reported for acute heart failure, gastrointestinal bleeding, acute pancreatitis, pulmonary embolism, aspiration pneumonia, nosocomial and community-acquired pneumonia; in addition, it was associated with the risk of developing diabetes (45-55). Regarding the predictive role of BUN in COVID-19, 3 possible mechanisms have been proposed: 1) direct kidney involvement and

virus invasion of kidney tissue, 2) hypoxic renal damage due to pulmonary involvement and hypoperfusion due to hypovolemia or heart involvement, and 3) septic and another type of shock and organ failure (56-62).

This study has some limitations. It was a retrospective study, and all data were limited to a referral university hospital. We included only cases with 30 days of hospitalization. We did not consider the time lag between the start of symptoms and hospitalization.

Conclusion

Blood urea nitrogen and CBC provide strong predictive clues about the prognosis of hospitalized COVID-19 patients, and rapid dynamic changes in the second week can predict a poor outcome in these patients.

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Ethical statement

This observational study was approved by the Ethics Committee of Golestan University of Medical Sciences, Gorgan, Iran
(Code: IR.GOUMS.REC.1399.031).

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

MF, MHTB, SMH, and AT designed the study. MHTB and AR collected data. MF, SMH, and AR analyzed data. MHTB, MF, VT and SMH prepared the manuscript. All authors read and approved the final manuscript.

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