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COVID-19 outpatients and surviving inpatients exhibit comparable blood test results that are distinct from non-surviving inpatients

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ABSTRACT

Aim: The decision of admitting COVID-19 patients as inpatients is mostly determined by chest X-ray based diagnosis of pneumonia severity. However, prognosis of inpatients may diverge into two groups, one group of inpatients did not survive while another group did.

Material and Method: More than 100 COVID-19 outpatients are collected from Tokat, Turkey in three categories: outpatients, surviving inpatients, and deceased inpatients. Their blood test profiles are analyzed and compared by dimension reduction techniques and classic statistical tests.

Results: We observe that surviving inpatients share a common blood test profile with the outpatients, whereas non-surviving inpatients are distinctively different. The non-surviving inpatients are on average older. Among patients older than certain age, non-surviving inpatients have higher neutrophil level, lower lymphocyte level (thus higher neutrophil/lymphocyte ratio), lower calcium level, higher C-reactive-protein, sodium, whole blood cell level, andlower hemoglobin level, than the surviving patients (whether these are inpatients or outpatients).

Conclusion: Surviving status is more important than in-and out-patient status in a patient's cluster membership based on blood test profile. This result suggests a plan to use both X-ray diagnosis and blood test results as a criterion to admit COVID-19 inpatients.

Keywords: COVID-19, outpatients, surviving, non-surviving, blood test results

INTRODUCTION

Since the end of 2019 and beginning of 2020, a new species of Coronavirus (called SARS-CoV-2), through person-to-person respiratory transmission, caused a global pandemic (called COVID-19). The scope of reach is so widespread that COVID-19 is often compared to the 100-year old 1918 H1N1 virus pandemic (1,2). COVID-19 also has a big impact on health system, as severe patients need oxygen, ventilation, and a bed in intensive care unit (ICU) for many days, if not weeks. On the other hand, many COVID-19 outpatients who have mild symptoms at the beginning may quickly lose body oxygen (hypoxia) and deteriorate towards potential death (3,4).

Because the decision to put a COVID-19 patient in hospital (inpatient) is based on an apparent symptom, such as severity of pneumonia, we ask if blood test results may provide a further and better assessment on whether a patient should be admitted to the hospital or not. A Turkish cohort of more than 100 COVID-19 patients were collected from the Tokat State Hospital to address this question . Our cohort contains 56% outpatients and 44% inpatients-though not exactly half-half, provides a reasonable representation of both group of patients. Previously, there are other publications to characterize the demographic and symptomatic differences between the inpatients and outpatients (5). Although we also have demographic information (e.g. age, gender), the focus of this paper is on blood test measurement based characterization of COVID-19 patients (6).

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There have been other Turkish COVID-19 datasets being analyzed, such as (7-13). However, none of these address the differences between the three groups, i.e., outpatients, surviving inpatients, and non-surviving inpatients. Our unique dataset can be used to simultaneously question the outpatient-inpatient distinction and surviving-deceased patient distinction.

MATERIAL AND METHOD

The COVID-19 patients were collected from the Tokat State Hospital. Ministry of Health permission and Tokat Gaziosmanpaşa University Ethics Committee permission were obtained (Date: 01.04.2021, Decision No: 83116987/377). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A patient was examined with X-ray tomography for pneumonia. Those with pneumonia are classified into three groups: light, moderate, and severe. Light pneumonia patients were sent home as outpatients. Moderate pneumonia patients were further examined with other diseases: those (1) with additional diseases and/or (2) with other risk factors were admitted to hospital as inpatients. Severe pneumonia patients were admitted to the hospital as inpatients.

Blood tests for outpatients were taken at the time when they came to the hospital. Blood test for inpatients were taken both at the time of arriving at hospital, or before receiving treatment in a following day. These nine blood test factors are included in this paper: C-reactive-protein (CRP), calcium, potassium, sodium, vitamin-D, white blood cell (WBC) count, lymphocyte cell count, hemoglobin (HGB) and neutrophil.

Dimension reduction: We use two methods for dimension reduction: (1) t-SNE (full name: t-distributed stochastic neighbor embedding) (14) and (2) UMAP (full name: uniform manifold approximation and projection) (15). One difference between these methods and the more traditional PCA (full name: principal component analysis) and MDS (full name: multi-dimensional scaling) is that different clusters are not linearly proportional to the actual dissimilarity between the clusters, but is reasonable spaced. When we only want to illustrate clusters, this feature becomes an advantage because we optimally use the graph space. Both t-SNE and UMAP are run by R (www.r-project.orh) packages: Rtsne and umap. In Rtsne, the default parameter values are used, including perplexity=30. It is the same for umap where we use the default setting, e.g., number of neighbor=15, and use of Euclidean distance. Both t-SNE and UMAP has a random component, so each run can be slightly different from another run. The scale and direction of the x and y axes of a t-SNE or UMAP plot do not have any meaning, and they are simply marked as (component) 1 and 2.

Statistical Analyses

All statistical analyses are carried out by R functions, include cor (correlation coefficient), cor.test (correlation test), anova (analysis of variance), t.test (t-test), wilcox.test (Wilcoxon test), lm (linear regression), glm(···, family="binomial") (logistic regression). The MAD (full name: median absolute deviate) is defined as MAD=median(abs(x–mean(x))), which can be considered as a non-parametric equivalence to standard deviation.

RESULTS

Basic statistics of the data (first order): All 76 outpatients survived, whereas 60 inpatients can be further split into two groups: n=45 who survived and n=15 who died. **Table 1** shows the mean and standard deviation of age and nine blood test measures, as well as the gender distribution, in these three groups. Generally, the factor value of the surviving inpatient group is in-between the mean values of the other two groups. For example, mean value for the C-reactive protein (CRP) of the surviving-inpatient group is 11.08, whereas that for the outpatient group is 7.97, and that for the deceased inpatient group is 61.7. We also see that this cohort of COVID-19 patients is mostly female.

Original data may not be completely characterized by the summary statistics. For example, one may think from the mean age that the patients are mostly middle-aged. In fact, there are three young patients of ages 1,5 (surviving inpatient), and 5 (outpatient). Also, if a factor's value does not follow a normal distribution, its mean value is not the middle-range value one would think. To illustrate this point, we calculate the median and median absolute deviation (MAD) of all factors in the three groups in **Table 1**. While for most factors, the median and mean are similar, for CRP in the first groups, median is much smaller than the mean.

Basic statistics of the data (second order): The second-order statistic of the dataset is the correlation between two factors. **Table 2** shows the Pearson correlation coefficient and the corresponding p-value, and non-parametric Spearman correlation (and the corresponding p-value). A p-value smaller than 0.005 is considered to be significant (16-18) and is marked with boldface in **Table 2**.

At this 0.005 significance level, HBG is correlated with 7 other factors considering either one of the Pearson/Spearman correlations; calcium is correlated with 6 other factors, age, WBC is correlated with 5 other factors each; etc. In **Table 2**, the vitamin-D factor is only correlated with gender (lower than female). However, it might be an artifact in data collection: inpatients were taking vitamin-D supplement when they were in hospital, which may increase their vitamin-D level.

Table 1. Demographic and serologic factors in the three groups

Mean/standard deviation, median/MAD, of all factors in three different groups					
Factor	**Outpatient**	**Inpatient (survived)**	**Inpatient (deceased)**	**Inpatient**	**All**
	n=76	**n=45**	**n=15**	**n=60**	**n=136**
Age (mean±sd)	49.7±17.8	53.98±23.3	74.47±9.06	59.1±22.46	53.85±20.45
(median±MAD)	50.5±12.5	58±18	76±3	69.5±11.5	55.5±17.5
female %	68.4%	75.6%	73.3%	75%	72.4%
C-reactive-protein (CRP)	7.97±20.19	11.08±25.54	61.7±70.81	23.09±45.72	14.58±34.49
	2.015±1.632	3.27±2.27	69.6±48.295	3.87±3.218	3.06±2.492
Calcium (mg/dL)	9.34±0.68	9.2±0.86	7.44±0.62	8.76±1.11	9.08±0.94
	9.365±0.385	9.21±0.36	7.41±0.49	8.99±0.725	9.24±0.52
Potassium	4.32±0.42	4.35±0.51	4.04±0.91	4.27±0.64	4.3±0.53
	4.225±0.25	4.37±0.31	3.71±0.36	4.265±0.44	4.23±0.315
Sodium	139.58±4.42	140.49±3.09	147.38±8.15	142.21±5.65	140.74±5.15
	139.35±1.8	140.7±2.3	147.8±2.5	141.35±3.35	140.1±2.3
Vitamin D	17.47±14.12	15.35±10.56	13.48±8.11	14.88±9.97	16.31±12.46
	14.135±6.425	13.07±7.35	12.4±5.42	12.735±7.01	13.985±6.73
White blood cell (WBC) (10^9/L)	6.63±2.24	7.43±4.38	13.55±5.13	8.96±5.26	7.66±4.03
	6.25±1.335	6.37±1.81	13.29±2.89	7.115±2.42	6.525±1.775
Neutrophil	4.43±2.04	5.14±4.25	12.25±4.83	6.94±5.37	5.53±4.04
	4.14±1.18	3.85±1.615	12.29±3.19	5.43±2.71	4.29±1.63
Lymphocyte	1.57±0.7	1.78±1.05	0.71±0.37	1.51±1.04	1.54±0.86
	1.55±0.53	1.69±0.345	0.58±0.24	1.4±0.49	1.45±0.51
Hemoglobin (HGB) (g/dL)	12.88±1.71	12.4±1.7	9.55±1.54	11.69±2.06	12.35±1.96
	13.15±1.05	12.4±0.8	9.7±0.7	11.85±1.45	12.6±1.1

MAD: Median absolute deviate, (outpatients, surviving inpatients, and deceased/non-surviving inpatients). For each factor, there are two lines of summary statistics. The first line is mean±standard deviation; the second line is median±MAD. The last two columns are the summary statistics for inpatients (combining the two sub-inpatient groups), and for all (combining all three groups).

Table 2. Correlation between any two factors. Two lines are used to show the second-order statistics

Correlation (Pearson/Spearman) and corresponding p-values of all pairs of factors										
	Age	**CRP**	**Cal**	**Pot**	**Sod**	**VitD**	**WBC**	**Neut**	**Lym**	**HGB**
Sex	-.13 (.12)	-.16 (.063)	-.01 (.94)	0 (.96)	.09 (.28)	-.26 (**.0027**)	-.07 (0.44)	-.08 (.37)	.07 (.4)	-.35 (**3.2e-5**)
	-.14 (0.11)	-.2 (.022)	.01 (.89)	-.01 (.88)	.18 (.031)	-.24 (.0061)	-.08 (.35)	-.1 (.23)	.03 (.72)	-.35 (**3.3e-5**)
Age	-	.27 (**.0018**)	-.49 (**1.7e-9**)	.07 (.44)	.23 (.0077)	-.05 (.55)	.29 (**.00073**)	.35 (**3e-5**)	-.35 (**3.8e-5**)	-.17 (.05)
	-	.22 (.011)	-.52 (**1.4e-10**)	.03 (.75)	.2 (.019)	-.04 (.65)	.24 (.0056)	.3 (**.00046**)	-.3 (**.00039**)	-.13 (.14)
CRP		-	-.18 (.039)	-.13 (.14)	.11 (.19)	.03 (.76)	.28 (**.0012**)	.3 (**.00046**)	-.12 (.18)	-.3 (**.00034**)
		-	-.09 (.32)	.01 (.93)	.14 (.1)	.11 (.22)	.15 (.088)	.12 (.16)	-.04 (.64)	-.12 (.17)
Cal			-	.07 (.44)	-.3 (**.00041**)	.21 (.017)	-.45 (**2.8e-8**)	-.53 (**2.5e-11**)	.38 (**4.7e-6**)	.41 (**5.8e-7**)
			-	.15 (.09)	-.17 (.05)	.17 (.048)	-.27 (**.0017**)	-.36 (**1.4e-5**)	.39 (**2.9e-6**)	.35 (**3.9e-5**)
Pot				-	-.13 (.12)	.06 (.52)	0 (.97)	-.02 (.83)	.06 (.51)	.04 (.63)
				-	-.06 (.52)	.01 (.91)	.03 (.69)	.02 (.86)	.07 (.4)	.08 (.36)
Sod					-	-.13 (.15)	.14 (.1)	.16 (.056)	-.13 (.14)	-.35 (**2.4e-5**)
					-	-.05 (.57)	.02 (.81)	0 (.97)	-.05 (.58)	-.31 (**.00023**)
VitD						-	-.01 (.88)	-.05 (.57)	.16 (.062)	.19 (.025)
						-	.06 (.5)	.05 (.58)	.12 (.17)	.16 (.059)
WBC							-	.97 (**4.8e-84**)	.01 (.87)	-.32 (**.00017**)
							-	.94 (**3.3e-63**)	.05 (.57)	-.3 (**.00044**)
Neut								-	-.22 (.0097)	-.36 (**2.3e-5**)
								-	-.23 (.0071)	-.3 (**.00044**)
Lym									-	.19 (.032)
									-	.26 (**.0023**)

The first line is Pearson correlation coefficient (cc) (and the corresponding p-value for testing cc=0); the second line is the non-parametric Spearman correlation (and the corresponding p-value). P-values smaller than 0.005 are marked with boldface. CRP: C-reactive-protein, cal: calcium, pot: potassium, sod: sodium, vitD: Vitamin D, WBC: White blood cells, neut: neutrophil, lym: lymphocyte, HGB: hemoglobin

Clustering pattern for three groups by dimension reduction: **Table 1** shows that the three groups: outpatients, surviving inpatients, and deceased inpatients potentially may have different blood test measures. To check this, we first consider each person as a point in the 9-dimensional space (for nine blood test variables, and note the age factor is not used), then project the points to low-dimensional space by a dimension-reduction technique. We use both t-SNE and UMAP, which are popular in single-cell expression data analysis as well as other fields (14,15,19-23).

Before applying the dimension reduction techniques, there is another pre-processing option. We can either use the original dataset, or, forcing each factorsto contribute equally in the high-dimensional space by standardizing a factor (zero-mean and unit-variance). Actually, only the scaling part (forcing variance to be 1) is relevant, while shifting the mean to zero does not affect the dimension reduction result. Since CRP factor value does not follow a normal distribution, during pre-processing, CRP is log-transformed first before scaling it. **Figure 1** shows four versions of the dimension reduction using t-SNE or UMAP, with or without standardization/scaling. Deceased samples are in red, surviving inpatients are in green, and outpatients are in blue. It can be seen that green and blue dots are not separated, whereas red dots are clustered, in particular for the standardized data.

Direct test of differences between three groups: To have a more direct proof on the differences between the three groups (outpatients, surviving inpatients, and deceased inpatients), three tests are carried out: (1) ANOVA which tests any difference between one or more groups from other groups; (2) t-test (or the non-parametric version: Wilcoxon test) between outpatients and surviving patients; (3) t-test (and Wilcoxon test) between the deceased inpatients and all surviving patients (both inpatients and outpatients). Gender is not a continuous value, but its proportion is not significant for any tests (p-values for (1) Fisher's test for 2-by-3; (2) Fisher's test between group-1 and 2; (3) Fisher's test between group-3 and combined groups 1 and 2, are 0.73, 0.53, and 1).

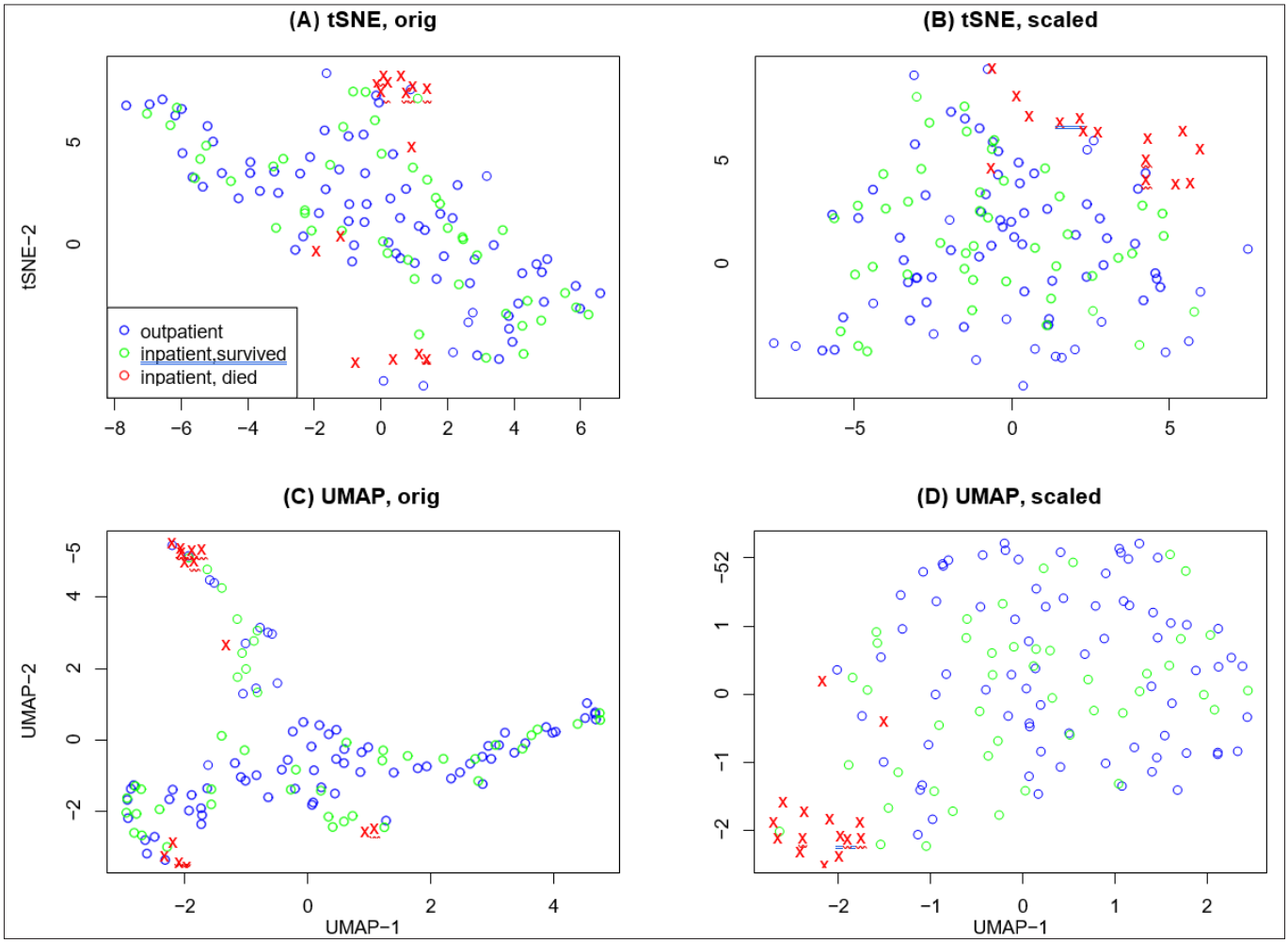

Figure 1. Projection of patient's blood test results from a 9-dimensional space to 2-dimension using two dimension-reduction techniques and/or with variable scaling (also, CRP factor is log-transformed before scaling): (A) t-SNE using the original data; (B) t-SNE after each variable is standardized to zero-mean and unit-variance; (C) UMAP using the original data; (D) UMAP using the standardized data. Red dots represent deceased inpatients, green for surviving inpatients, and blue for outpatients (all survived).
tSNE: t-distributed stochastic neighbor embedding , UMAP: uniform manifold approximation and projection orig: original

Table 3 shows the results of these three tests for nine blood test factors as well as age. For ANOVA test, all factors are significant at 0.005 level except potassium and vitamin-D. We have already mentioned that inpatients took vitamin-D supplement as soon as they were admitted to the hospital; this may provide a short-term boost to their vitamin-D level. Similarly, the potassium level can change quickly, within 5-6 hours. A more careful investigation would be to follow up the potassium level through time, and for this additional analysis with more data is needed.

Table 3. Various test results between groups for each factor

t-test/Wilcoxin-test, ANOVA, conditional (on age) logistic regression, p-values				
Factor	**Out vs surv-in**	**(out+surv-in) vs deceased**	**ANOVA**	**LR (cond on age)**
Age	0.291/0.155	**3.76e-9/1.41e-5**	**5.95e-5**	
(log) CRP	0.174/0.186	**0.0011/0.000153**	**1.67e-5**	**0.00324**
Calcium	0.366/0.276	**1.6e-9/2.85e-9**	**6.47e-15**	**5.91e-5**
Potassium	0.693/0.637	0.238/0.0161	0.118	0.11
Sodium	0.188/0.0732	**0.0033/3.84e-5**	**1.12e-7**	**0.00182**
Vit-D	0.353/0.409	0.197/0.457	0.434	0.626
WBC	0.257/0.942	**0.000185/1.48e-6**	**5.24e-10**	**0.00162**
Neutrophil	0.304/0.752	**2.54e-5/5.02e-8**	**2.99e-13**	**0.00056**
Lymphocyte	0.254/0.298	**5.28e-9/1.24e-6**	**0.00011**	**0.000422**
HGB	0.139/0.0568	**6.3e-7/2.57e-7**	**9.76e-10**	**0.000203**

The second column is the t-test/Wilcoxon-test p-value between outpatients and surviving inpatients. The third column is those between non-surviving inpatients and surviving patients (but in-and out-patients). The fourth column is the p-value for analysis of variance (ANOVA). The last line is logistic regression of dead/alive status over a factor conditional on age. P-values smaller than 0.005 are marked with boldface. The values for CRP factor are log-transformed before a test. out: outpatient, surv-in: surviving patients, cond: conditional, LR: Logistic regression, vit-D: vitamin-D, WBC: White blood cell, HGB: Hemoglobin

Table 3 also shows that the significant ANOVA test results are all due to the difference in the deceased group, not between the inpatient (if they survive) and outpatient group. In other words, the separation between inpatients and outpatients is more artificial, whereas that between the surviving and non-surviving patients is more real. There are only two factors that show a potential trend (at the 0.1 level): sodium level is higher, and HGB is lower, for (surviving) inpatients than outpatients. Since these trends are not statistically significant at a level we feel confident, more data is needed to confirm or reject the observation.

To summarize our observations (**Tables 1** and **3**): when compared to the surviving patients whether they are inside or outside the hospital, deceased inpatients are older, higher CRP, white blood cell, neutrophil, and lower calcium, lymphocyte cell, hemoglobin. These differences collectively (excluding age) lead to a distinct group of non-surviving inpatients that are separated from surviving patients (both outpatients and inpatients), as shown in **Figure 1**.

Contribution of a factor to the surviving status conditional on age: Table 3 shows that almost all blood test factors are associated with the surviving status of a patient. However, the age is also associated with surviving status. Is a factor associated with surviving status because older patients tend to have different level of that factor? To address this question, we carry out a logistic regression: (death)~(factor)+(age).

The last column in **Table 3** shows the p-value for the conditional logistic regression where the effect of age is corrected. Although all p-values increase, the originally significant factors are still significant at 0.005 level. We conclude that these associated factors cannot be explained solely by the age differences in deceased and surviving patients.

Neutrophil-to-lymphocyte ratio (NLR) as a survival biomarker: Neutrophil-to-lymphocyte ratio (NLR) has been used as a biomarker for COVID-19 disease prognosis (24-27). Instead of using the NLR, we plot our data using only two factors: lymphocyte as x-axis and neutrophil as y-axis, in **Figure 2A**). It can be seen that similar to **Figure 1B,D**, **Figure 2A** also separates the deceased inpatients from both surviving inpatients and outpatients. A straight line going through the origin represents points with a constant NLR (the slope). We mark the NLR=10 line in **Figure 2A**, which reasonably separates red and green/blue dots. With this line, three red dots are misclassified, or 3/15=0.2 error rate; and 3-4 green/blue dots are misclassified, or ~0.03 error rate, including one surviving inpatient with a very large NLR value.

To add age information on topic of NLR, **Figure 2B** shows the scatter plot with age and NLR as two axes. **Figure 2B** essentially contains information from 3 variables, versus **Figure 1** and **Figure 2A** which use information from 9 and 2 variables. **Figure 2B** clearly shows that NLR is high mostly within a limited age range (around age of 80). It also validates our previous result that older age itself is not 100% responsible for poor prognosis, but partially. Besides older age, other factors such as NLR also contribute greatly to the poor outcome of COVID-19.

Other biomarkers for prognosis: Table 2 shows that calcium level is correlated with both neutrophil and lymphocyte level. To show that calcium is also correlated with NLR, **Figure 2C** shows the scatter plot of the two, confirming that higher NLR is associated with low calcium level. **Table 3** also shows that calcium is associated with age, which again can be shown directly, in **Figure 2D**. Similar observation was shown in the literature, e.g. (28).

Figure 3 shows the rest of factors that are significantly associated with the non-survival status according to **Table 3**: CRP, sodium, WBC, and HGB (neutrophil and lymphocyte are combined into a ratio in **Figure 2B** and calcium in **Figure 2D**). All these plots show an interplay between these factors and age i.e., those non-surviving patients are predominately above certain old age; then, higher or lower level of these factors are, with various degrees, associated with the non-survival status (29). All these factors have been discussed in the COVID-19 literature: e.g., CRP, sodium and others, WBC, and HGB (30-33).

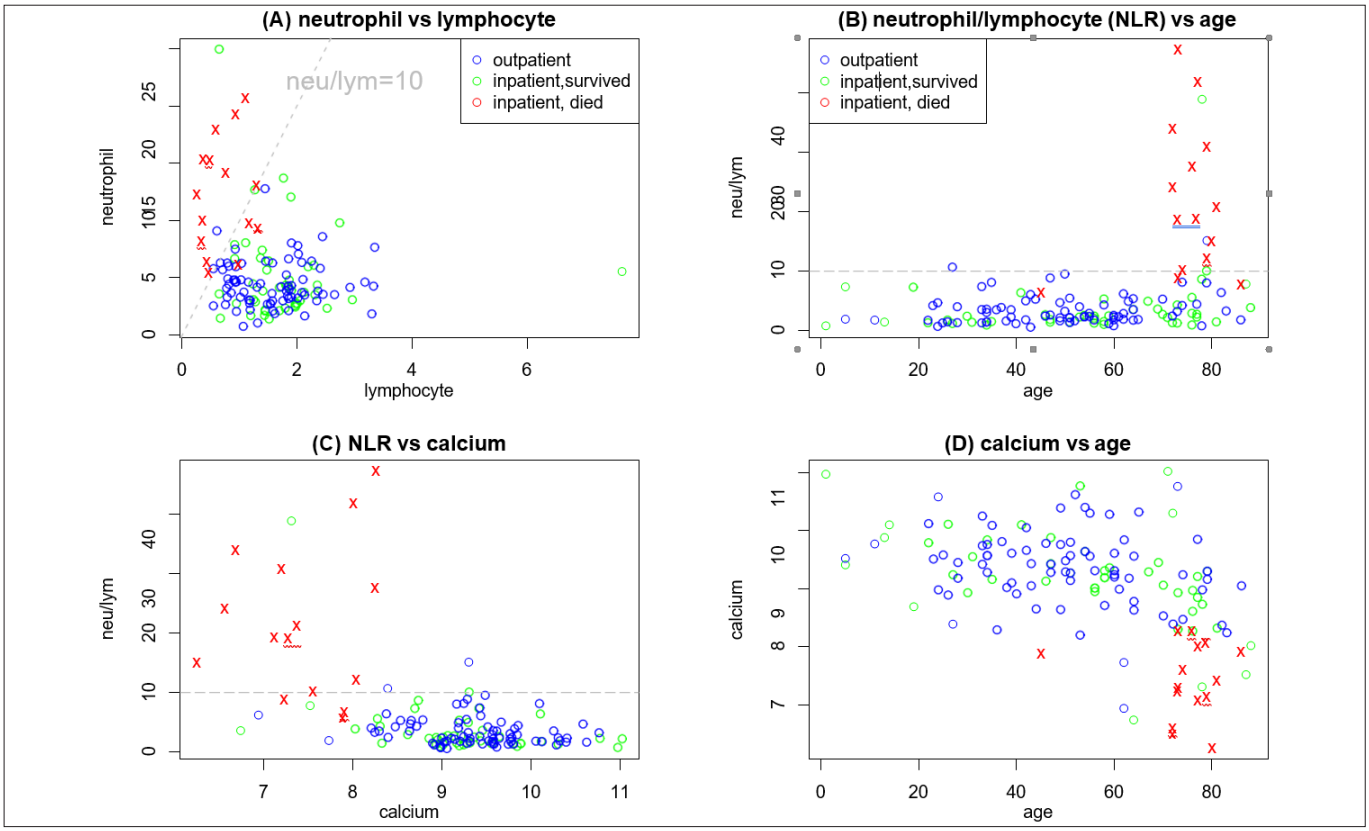

Figure 2. Scatter plots of (A) x=lymphocyte, y=neutrophil; (B) x=age, y= neutrophil/lymphocyte ratio (NLR); (C) x=calcium, y= NLR; (D) x=age, y= calcium. Samples in three different groups are marked with different colors: red for non-surviving inpatients, green for surviving inpatients, and blue for outpatients. NLR: neutrophil-to-lymphocyte ratio

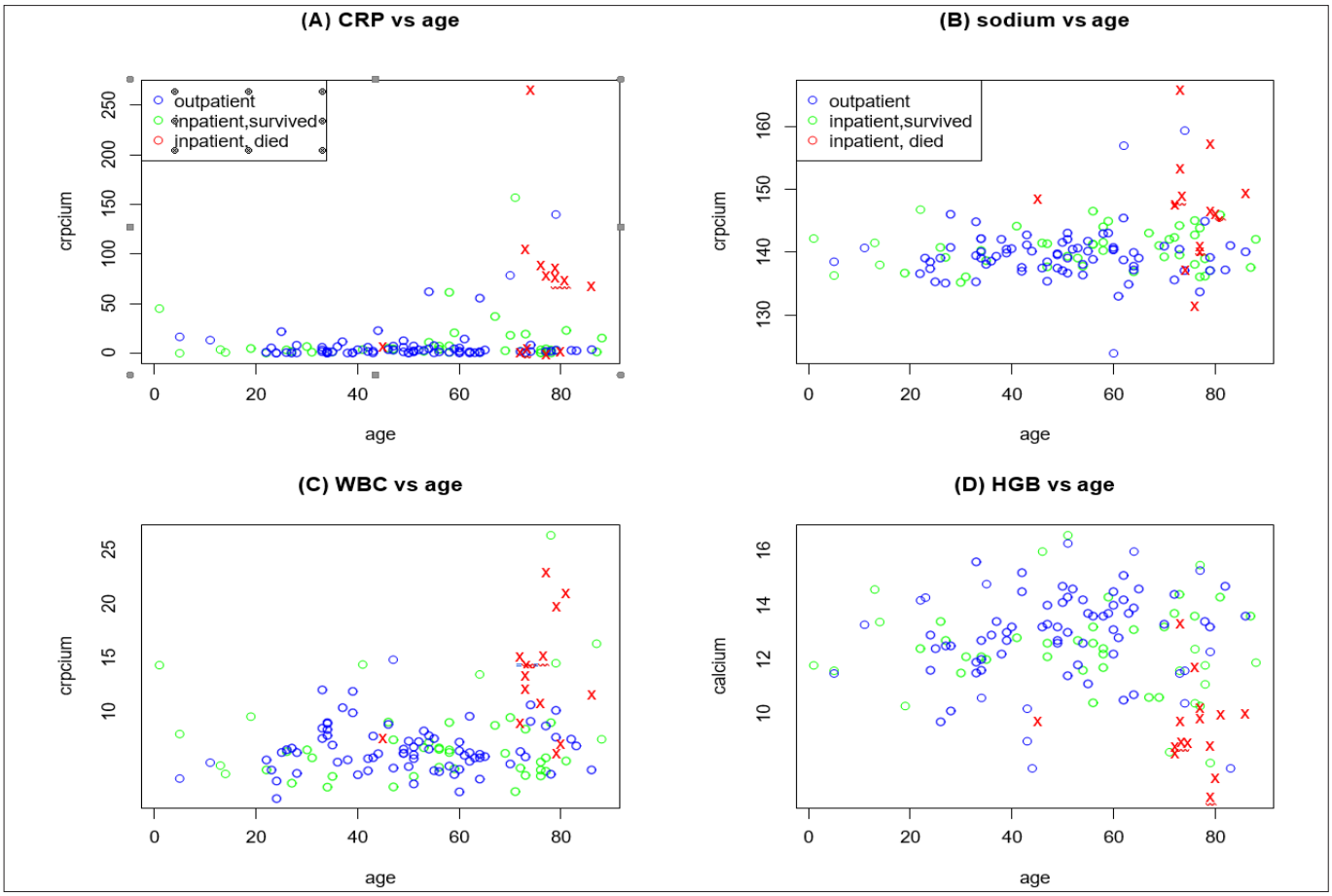

Figure 3. Scatter plots of factors over age: (A) CRP; (B) sodium; (C) white blood cell (WBC); (D) hemoglobin (HGB). Similar to Figure 2, red, green, blue represents deceased inpatients, survived inpatients, and outpatients. CRP: C-reactive-protein WBC: White blood cell, HGB: Hemoglobin

DISCUSSION

It is common to project a multi-factor (high-dimensional) dataset to a two-dimensional plane to examine if there are clusters and sub-clusters. However, it is less discussed in the literature whether the data needs a preprocessing. In particular, whether each factor/variable should contribute equally to the high-dimensional distance between samples is a crucial consideration in preprocessing. To standardize factors, i.e., to make each factor to have zero-mean and unit-variance, would treat all factors equally. Closely related to issue of standardization, for non-normal distributions such as exponential or one-sided decaying distributions, the two parameters of mean and variance do not really characterize the distribution well, and it is desirable to transform the variable (e.g. log-transformation) to make the distribution normal-like.

Figure 1 shows that standardization (not the zero-mean part, but the unit-variance and some log-transformation the nine blood test measurement factors part) leads to a much better separation of the deceased samples (**Figure 1B,D**) compared to those without the standardization (**Figure 1A,C**). From our example, we recommend the standardization preprocessing step when multiple factors are considered jointly.

Our results show that among patients older than certain age, non-surviving inpatients have higher neutrophil level, lower lymphocyte level (higher NLR), lower calcium level, higher CRP, sodium, WBC, and lower HGB level, than the surviving patients; whether these are inpatients or outpatients. Comparing the two associated factors, CRP and HGB, there had been reports linking CRP level to severity of COVID-19 disease, and discussion on how anemia affects the quality of life in elder COVID-19 patients (34-36). Interestingly, Lippi et al pointed out that hemoglobin level may decrease in severe COVID-19 patients but the cause-effect direction is unclear (37).

In addition to CRP and HGB, calcium, potassium, sodium, WBC, neutrophil, lymphocyte cell count and Vitamin-D are extensively discussed in the literature (38-50). All of these factors except Vitamin D and potassium show significant differences between non-surviving and surviving patients in **Table 3** and are discussed in the literature, which confirm our findings and indicate dysregulation in COVID-19 patients.

The fact that surviving inpatients share more blood test results in common with outpatients than the non-surviving inpatients has direct implication to patient management. Outpatients should carry out self-risk assessment (www.uptodate.com/contents/covid-19-outpatient-evaluation-and-management-in-adults), and use cheap repurposing drugs. The treatment of outpatients has been evolving constantly. Patients visiting a hospital will go through medical examination to determine if they are in enough danger to stay in hospital. The main conclusion and lesson from this paper is that it is beneficial to not just use chest X-ray diagnosis alone, but also use blood test results, in screening COVID-19 patients for risk.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ministry of Health permission and ethics committee permission at the Tokat Gaziosmanpasa University were obtained (Date: 01.04.2021, Decision No: 83116987/377).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

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