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Predicting COVID-19 Hospitalized Patients' Outcome with Homocysteine

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In October 2020, we published '*Homocysteine as a potential predictor of cardiovascular risk in patients with COVID-19*' [1]. Since then, recent scientific evidence from other authors [2-6], together with our own continuing research to include a larger cohort of hospitalized COVID-19 patients [7], has supported our original hypothesis, confirming that homocysteine (Hcy) is a predictive marker of COVID-19 outcome.

The COVID-19 pandemic has provoked a global, rapid increase of cases due to the high infectivity of the etiological agent, COVID-19 virus. In February 2021, over 110 million confirmed COVID-19 cases with 1 million deaths were reported worldwide (www.who.int).

Since the beginning of the pandemic, the identification of reliable biomarkers for COVID-19 disease progression has been a great challenge. Among various biomarkers tested, Hcy has sparked particular interest due to its association with both the metabolism of the SARS-CoV-2 virus and cardiovascular complications, which have proven to be the main cause of death among COVID-19 patients [8-10].

It is known that the SARS-CoV-2 virus transfers methyl group for viral RNA capping, from the host cell S-adenosylmethionine (SAM) converted into S-adenosylhomocysteine (SAH). SAH hydrolase (SAHH) removes adenosine from SAH, and produces an intermediate product called "homocysteine," which is recycled by remethylation and the trans-sulphuration pathway in the human body [5,6,11,12].

Recently, novel regulatory mechanisms directly involved with Hcy in the activation of angiotensin II type receptor have been described [13]. Ferroptosis, a newly identified form of regulated cell death, does not share morphological, biochemical, or genetic similarities with other forms of regulated cell death, such as apoptosis [14]. It is characterized by the accumulation of iron and lipid reactive oxygen species (ROS) and by smaller mitochondria with condensed membrane densities. Increasing evidence suggests that ferroptosis dysfunction is positively related to several human diseases, including tumorigenesis [15]. Ferroptosis was found to be linked to common symptoms of COVID-19 disease, namely neurological disturbances, including cognitive impairment, ageusia, and anosmia

(taste and smell loss) [16].

Regarding the genetic background of Hcy metabolisms, the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism. The MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which produces methyl donor for the conversion of Hcy to methionine [17].

Hcy has been reported as a potential predictive biomarker for COVID-19 infection severity in many studies [1-4]. In a series of 273 Chinese hospitalized patients with mild COVID-19 disease, over 40 parameters were measured at admission. Disease progression was registered for 72 patients (computed tomography [CT] lung scans) and age, Hcy plasma levels and monocyte-to-lymphocyte ratio (MLR) were the only significant predictors in hyperhomocysteinemic patients (>15.4 μmol/L), estimated to correspond with a three-fold increased risk of disease evolution at radiological images. Interestingly, Hcy is the only predictive marker identified which is readily modifiable. Further, recent data confirmed the value of Hcy (together with age, MLR, and time from disease onset to hospital admission) in predicting the risk of severe pneumonia (on chest CT scan). The authors did not report any other additional organ involvement [3].

Our retrospective cohort study, including 313 COVID-19 hospitalized patients (female 34.8%; mean age 62 years) between April-September 2020, also included a broad panel of clinical laboratory data collected at admission. Of the enrolled patients, 10.9% died during hospitalization (3% were transferred to other hospitals and were lost to follow-up). Hcy was found to be the strongest predictor of Covid-19 critical-progression leading to death. Univariate analysis demonstrated that age (OR 1.04), Hcy (OR 1.06), and Neutrophil/Lympocyte count ratio (OR 1.03) were significant predictors of critical progression leading to death and RBC (OR 0.68) and Lymphocytes count (OR 0.23) with benign outcome (Table 1). ROC analysis

		Status[a]		**Univariate Analysis**		
Epidemiologic and clinical characteristics:	Total (n=313)	Dead (n=34. 11.2%)	Alive (n=270. 86.3%)	OR	95% CI	p-value
Gender, M	204 (65.2)	22 (64.7)	175 (64.8)	0.89	(0.50-1.57)	0.690
Age, Median (1Q-3Q)	62 (50-74)	73 (64-78)	60 (49-73)	1.02	(1.01-1.04)	0.002
Citizenship[b]						
Italians	256 (82.8)	34	213	ref		
Foreigners	53 (17.2)	0	25	1.57	(0.70-3.53)	0.271
Status[a]						
Alive	270 (86.2)	-	270 (100)	ref		
Dead	34 (10.9)	34 (100)	-	3.08	(1.45-6.51)	0.003
Unknown	9 (2.9)	-	-			
Ln Homocysteine (μmol/L)	2.4 ± 0.5 (-0.4-4.4)	2.6 ±0.8 (1.4-4.4)	2.4 ±0.5 (-0.4-3.9)	-		
Ln D-dimer (ng/mL)	6.7 ± 1.4 (2.3-10.6)	7.7 ±0.9 (5.9-9.5)	6.5 ±1.3 (2.3-10.5)	1.05	(0.61-1.29)	0.605
Ln PT (s)	1.4 ± 1.7 (-3.1-4.6)	3.8 ±0.4 (3.2-4.7)	3.4 ±0.8 (-0.6-4.7)	0.79	(0.55-1.14)	0.333
Ln aPTT (s)	1.4 ± 1.7 (-3.1-4.6)	1.3 ±1.8 (-0.1-4.6)	1.3 ±1.7 (-3.1-3.8)	0.86	(0.72-1.04)	0.121
Ln Fibrinogen (mg/dL)	6.0 ± 0.4 (2.9-7.3)	6.1 ± 0.4 (4.6-6.9)	6.0 ± 0.4 (2.9-7.3)	0.74	(0.41-1.35)	0.326
Ln BNP (pmol/mL)	4.6 ± 1.7 (1.65-10.6)	6.2 ± 1.7 (3.7-10.2)	4.5 ± 1.7 (1.6-10.6)	1.33	(1.11-1.59)	0.002
Ln CK (U/L)	4.3 ± 1.1 (0.6-8.4)	4.5 ± 1.4 (2.8-7.7)	4.3 ± 1.1 (0.6-8.4)	0.89	(0.69-1.14)	0.342
Ln Troponin (ng/L)	-0.5 ± 3.6 (-6.9-7.7)	2.3 ± 0.8 (0.4-3.2)	-1.0 ± 3.5 (-1.8-6.2)	0.99	(0.91-1.07)	0.785
Ln Red Blood Cells (10^6/L)	1.4 ± 0.5 (-1.8-6.2)	1.3 ± 0.2 (0.6-1.9)	1.4 ± 0.6 (-1.8-6.2)	1.00	(0.63-1.61)	0.979
Ln White Blood cells (10^9/L)	1.9 ± 0.6 (-1.7-4.7)	2.1 ± 0.6 (00.4-3.2)	1.9 ± 0.6 (-1.7-4.7)	1.10	(0.72-1.67)	0.672
Ln Neutrophils (10^9/L)	1.7 ± 0.7 (-0.3-4.7)	1.9 ± 0.7 (0.3-3.0)	1.4 ± 0.9 (-2.9-4.6)	1.22	(0.82-1.81)	0.320

Ln Lymphocytes (10^9/L)	0.1 ± 0.7 (-2.2-4.9)	-0.3 ± 0.6 (-2.2-0.5)	0.1 ± 0.7 (-1.7-4.9)	0.99	(0.68-1.44)	0.153
Ln Neutrophils/ Lymphocytes	1.5 ± 0.9 (-2.9-4.6)	2.3 ± 0.8 (0.3-3.8)	1.4 ± 0.9 (-2.9-4.6)	1.12	(0.84-1.51)	0.141
Ln Monocytes (10^9/L)	-0.8 ± 0.7 (-3.5-2.2)	-1.1 ± 1.0 (-3.5-0.1)	-0.8 ± 0.7 (-2.9-2.2)	1.30	(0.91-1.87)	0.153
Ln Monocytes/ Lymphocytes	-0.9 ± 0.7 (-5.2-1.7)	-0.7 ± 0.8 (-2.3-0.4)	-1.0 ± 0.7 (-5.2-1.7)	1.33	(0.91-1.93)	0.137
Ln Eosinophils (10^9/L)	-2.9 ± 1.1 (-5.5-0.1)	-3.3 ± 1.3 (-4.6-0.1)	-2.9 ± 1.1 (-5.5-0.2)	1.07	(0.81-1.47)	0.562
Ln Basophil (10^9/L)	-3.6 ± 1.3 (-6.9-6.1)	-3.3 ± 2.0 (-4.6-5.7)	-3.6 ± 1.2 (-6.9-6.1)	0.94	(0.70-1.25)	0.656
Ln Platelet (10^9/L)	5.4 ± 0.6 (-2.3-6.6)	5.2 ± 0.6 (3.1-6.1)	5.4 ± 0.6 (-2.3-6.6)	0.80	(055-1.18)	0.260
[a]9 cases unknown; [b]4 data missing; Data are presented as mean ± SD and number (n) of patients (%), as appropriate.						

Table 1: Descriptive epidemiological and clinical features of hospitalized COVID-19 patients. A comparison between survivors and non-survivors characteristics and univariate analysis of predictive markers for in-hospital mortality.

indicated Hcy cut off of 16 µmol/L for predicting COVID-19 infection outcome (sensitivity 40% and specificity 84%); patients with Hcy levels >16 µmol/L had significantly increased risk of in-hospital mortality (p=0.002) both as a continuous and dichotomic value. Our results demonstrate that Hcy is an effective predictive biomarker for hospitalized COVID-19 patients' outcome.

Several studies have demonstrated the importance of vitamin supplementation in patients with the COVID-19 disease. Vitamin B supplements (especially B9 and B12) are able to normalize blood Hcy levels in both apparently healthy individuals and patients with a history of stroke or Parkinson's disease [18-20]. It is reasonable to suggest that B vitamins and Folic acid integration may have protective clinical effects for patients with infectious disease, due to *MTHFR* 677T allele alteration or other pathologic conditions. The relationship between the prevalence of genetic polymorphisms of *MTHFR C677T* and COVID-19 incidence and mortality rates seems to be intriguing; it may be useful biomarker COVID-19 infection severity stratification and it may be used for preventive medical treatments and supplementations.

Hyper-homocysteinemia is related to many virus infection outcomes, including human hepatitis virus [21], human papilloma virus [22] and Human immunodeficiency virus [23,24]. B vitamins (B2, B3 and B6) have a key role in the enhancement of the immune system [25].

Even though Hcy has been proven as a critical biomarker of cardiovascular risk and complications in hospitalized COVID-19 patients, it has not yet been adopted in prospective studies for useful laboratory markers for the stratification of COVID-19 patients.

Hcy may be a valuable biomarker which can help clinicians identify patients who are at higher risk for severe COVID-19 infection. Hcy plasma levels are easily determined by a simple and affordable laboratory test. The association between Hcy levels >16 µmol/L and worse COVID-19 prognosis should encourage preventive health programs aimed to supplement dietary group B vitamins and folic acid for COVID-19 patients.

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