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Effects of Remdesivir and Favipiravir on Red Cell Indices of COVID-19 Patients

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Abstract

OBJECTIVES: Both absolute and restrictive iron deficiency with a highly ferritin level has been observed in COVID-19 patients. Remdesivir and Favipiravir are currently used in the management of COVID-19 without clinical or laboratory evidence that these drugs are potentially harmful to the blood elements. This study aims at the determination of the effect of remdesivir and favipiravir on the red cell indices that discriminate the absolute from restrictive iron deficiency.

MATERIALS and METHODS: A total number of 149 COVID-19 patients were included in this cross-sectional study; 70 patients were treated with health care (Group I); 17 patients were treated with remdesivir (Group II); and 62 patients were treated with favipiravir (Group III). Complete blood count, red cell indices, C-reactive protein, and D-dimer were determined as primary outcomes.

RESULTS: There are no significant differences in the hematological indices, C-reactive protein, and D-dimer between treated groups. Significant differences between the studied groups who have been observed in the Lal and Shine index, and England and Fraser's index. The red cell indices of patients treated with remdesivir indicated that the patients have significantly restrictive iron deficiency compared with patients treated with favipiravir. These changes are not related to the d-dimer levels.

CONCLUSION: Patients treated with favipiravir showed improvement of the iron utilization by tissues as the percentage of patients who have restrictive iron deficient is lower than the corresponding percentage of absolute iron deficiency compared with patients treated with remdesivir.

Keywords: COVID-19, remdisivir, favipiravir, absolute iron deficiency, restrictive iron deficiency

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تأثيرات ريمديسفير وفافيبيرافير على مؤشرات كريات الدم الحمر عند مرضى كوفيد - 19

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المستخلص

الأهداف: تم ملاحظة كل من فقر الحديد المطلق والمقيد المصاحب بأرتفاع مستويات عنصر فريتين عند مرضى كوفيد-19 . يعالج كوفيد-19 بكل من ريمديسفير و فافيبيرافير من دون ملاحظة شواهد سريرية او مختبرية في كونها لها تأثيرات مضرة على مكونات الدم. هدفت الدراسة الى تحديد تأثيرات ريمديسفير و فافيبيرافيرعلى مؤشرات كريات الدم الحمر وذلك لتمييز فقر الحديد المطلق عن المقيد.

المود وطرائق العمل

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معلومات البحث
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ضمت الدراسة المقطعية 149 مريض كوفيد-19 ، 70 مريضا عولجوا بالعناية الصحية (مجموعة 1) ، 17 مريضا عولجوا بريمديسفير (مجموعة 2) و62 مريضا عولجوا بفافيبيرافير (مجموعة 3). تم تحديد أعداد عناصر الدم ، مؤشرات كريات الدم الحمر، البروتين التفاعلي- C و ثنائيات D كمحصلات اولية .
النتائج
لم تسجل فروقات ذات دلالة نوعية متميزة في مؤشرات الدم والبروتين التفاعلي- C و ثنائيات D بين المجاميع المعالجة. لوحظ اختلاف في مؤشرات لان وشان و انكلاند وفراسير ذات دلالة نوعية بين المجاميع المعالجة. دلت النتائج على لن المرضى المعالجين بريمدسسفير يتصفون بدلالة نوعية متميزة بفقر الحديد المقيد مقارنة بالمعالجين بفافيبيرافير وان هذه التغيرات ليست لها علاقة بمستويات ثنائيات D.
الأستنتاج
أظهروا المرضى المعالجين بفافيبيرافيرعن تحسن في استغلال انسجة الجسم للحديد حيث ان نسبة المرضى الذين يتصفون بفقر الحديد المقيد هي أقل من نظيرتها عند فقر الحديد المطلق مقارنة بالمرضى المعالجين بريمديسفير.

الكلمات المفتاحية : كوفيد-19، ريمديسفير، فافيبيرافير، فقر الحديد المطلق، فقر الحديد المقيد

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which presented with a broad spectrum of clinical signs and symptoms and ending with a multiple organ dysfunction syndrome. Anemia is a clinical feature or a laboratory finding of COVID-18.[1] A low hemoglobin level was associated with a significant elevation of serum ferritin level, indicating that the type of anemia is absolute iron deficiency anemia.[2,3] Studies showed that both low hemoglobin levels and high serum ferritin levels are predictors of poor outcomes.[4,5] The high serum ferritin levels are the outcome of inflammation induced by SARS-COV-2, which inducing a defect in the erythropoiesis.[6,7] Restrictive or functional iron deficiency anemia was also reported in COVID-19 patients, which presented with low hemoglobin levels and low or within normal limits of serum ferritin levels. Antivirals used in the management of COVID-19 are not free from the adverse reactions on the blood elements. Remdesivir is a nucleotide (adenosine) analog prodrug, had been granted in the United States on May 1st, 2020 to treat severe COVID-19.[8] Remdesivir is a safe drug and currently, there is no evidence that this drug adversely affected the hemopoietic system.[9,10] Favipiravir is an oral guanosine analog antiviral drug that inhibits the RNA-dependent RNA-polymerase enzyme, used in the management of COVID-19.[11] This drug is contraindicated in pregnant women because it is a teratogenic and embryotoxic agent.[12,13] Red cell indices are currently used to differentiate between absolute and restrictive iron deficiency anemia. Some of these indexes are; Mentzer, Shine and Lal, England and Fraser, Srivastava, Green and King, Ricerca, Sirdah et al, Ehsani, mean density hemoglobin per liter, and mean cell hemoglobin concentration.[14-23] The rationale of this study is antiviral drugs reduced the viral load, and subsequently, attenuate the inflammatory cytokines that reduced the level of hemoglobin. This cross-sectional study aimed to assess the red cell indexes in an attempt to clarify the type of anemia whether absolute or restrictive iron deficiency anemia in COVID-19 patients treated with remdesivir or favipiravir or health care management.

Materials And Methods

This multi-center cross-sectional study was conducted in the Department of Pharmacology, College of Medicine, The University of Diyala in cooperation with the Al-Kut University College in Wasit and Hawler Medical University in Iraq from January 1st, to June 30th, 2021. This study was registered by the institutional scientific committee according to the declaration of "Helsinki that the health of my patient will be my first consideration" The eligible patients are COVID-19 patients of both sexes aged >18 years. The criteria of inclusion are COVID-19 patients admitted in two different hospitals and treated with health care supportive medicines, supplemented with remdesivir or favipiravir, and they were recovered from their illness. The patients under the treatment with antiviral therapy were completed a 10-day course of remdesivir 200 mg, intravenously on day 1, followed by 100mg daily for the next nine days, or treated with oral favipiravir 1800mg loading oral dose on day 1, followed by 800mg daily for the next 13 days. All the patients were monitored for adverse reactions, and laboratory investigations of liver and kidney function tests, patients with saturated oxygen less than 90%, renal or liver diseases, and within normal range serum ferritin levels, non-survivors were excluded from the study. The therapeutic regimen of each antiviral therapy was according to the guideline of each hospital and the experience of the specialist. The red cell determinants at the end of antiviral treatment are the primary outcome measures. Red cell indexes that discriminate absolute from restrictive iron deficiency anemia were calculated as shown in Table 1. The sample size of the participants was calculated by using Gpower version 3.1software. A total number 149 patients (94 males and 55 females were included in this study. The patients were grouped according to their management into:

Group I (n=70): patients treated with health care

Group II (n=17): patients treated with health care and remdesivir

Group III (n=62) patients treated with favipiravir

Table 1: Calculated Red Cell Indices and Their Reference Values

Red cell indices	Year	Calculated formula	Reference values of iron deficiency	
			Absolute	Restrictive
Mentzer index[14]	1973	MCV/RBC	>13	<13
Shine and Lal index[15]	1977	$\frac{MCV \times MCV \times MCH}{100}$	>1530	<1530
England and Fraser index[16]	1973	MCV-(5×Hb)-RBC-3.4	> 0	< 0
Sirvastata index[17]	1973	$\frac{MCH}{RBC}$	>3.8	<3.8
Green and King index[18]	1989	$\frac{MCV \times MCV \times RDW}{HB \times 100}$	>65	<65
Red distribution width index	1987	$\frac{MCV \times RDW}{RBC}$	>220	<220
Ricerca index[19]	1987	$\frac{RDW}{RBC}$	>4.4	<4.4
Mean density of hemoglobin/liter-index[22]	1999	$(\frac{MCH}{MCV}) \times RBC$	<1.63	>1.63
Mean cell hemoglobin density-index[23]	1999	$\frac{MCH}{MCV}$	<0.3045	>0.3045
Sirdah[20]	2007	MCV-RBC-(3×Hb)	>27	<27
Ehsani[21]	2005	MCV- (10×RBC)	>15	<15

RBC: red blood cell count; Hb: hemoglobin, MCV; mean cell volume, MCH; mean concentration hemoglobin, RDW; red distribution width.

Statistical Analysis

The results of this study are presented as a number, percentage, median, and mean ±SD. The data were analyzed by using a two-tailed one-way analysis of variance (ANOVA), and a *post hoc* Bonferonni test to compare between a two- independent sample. A p-value of ≤0.05 is the cutoff significant level. Excel software version 10, and SPSS version 24 (IBM compatible) were used for statistical analysis.

Results

Table 2 shows the characteristic features of the participants. There is no significant difference between the groups of patients in the sex distribution. The median age of patients who belonged to Groups II and III was higher than the corresponding median age of Group I patients. A total number of 88 (59.1%) patients had a history of hypertension and 65(43.6%) patients with diabetes mellitus. There is no significant difference between groups of patients in the distribution of the associated concomitant diseases. Non-significant differences in white cell and differential count, blood platelet, inflammatory indices, and D-dimer values between the groups of patients (Table 2). Table 3 showed non-significant differences in the red cell indices measured by the hematological analyzer and the values are with normal reference values. The mean ± SD of the Shine and Lal index is significantly higher in the patients of Group II and III compared with the corresponding value of the Group I patients (Table 3). Patients treated with favipiravir showed the positive value of the England and Fraser index, indicating absolute iron deficiency which is significantly higher than the corresponding values of Groups I and II that showed negative value, indicating restrictive iron deficiency (Table 3). Remdesivir-treated patients (Group II) showed a significantly lower negative value of the England and Fraser index compared with the corresponding value of the patients managed with health care supportive measures (-103.1±58.0 versus -44.93±10.5). Table 4 shows a non-significant difference between Group I and Group II patients in the calculated red cell indices which indicated the status of red cell iron. Patients treated with favipiravir (Group III) showed a significantly low number of patients with Shine and Lal index indicating restrictive iron deficiency and a high number of patients with England and Fraser's index indicating absolute iron deficiency compared with the Group I patients. Faviripavir treated patients have a significantly higher number of patients with the England and Fraser's index indicating absolute iron deficiency compared with remdisivir-treated patients (Group II). The mean total percentage of Group I patients with red-cell indices indicating restrictive iron deficiency is 41%, in Group II is 44.7% (p=0.387), and in group III is 32.1%. The percentage of patients with red cell indices indicating restrictive iron deficiency is significantly lower in Group III compared with Group I and II patients. A significant association between the level of D-dimer of >0.4 with the absolute iron deficiency was observed in Group I and II patients (Table 5).

Table 2: Characteristics of the Participants

Determinants	Group I (n=70)	Group II (n=17)	Group III (n=62)	One-way ANOVA		*Post hoc* Bonferroni		
				F-value	p-value	P1	P2	P3
Sex (male: female)	44:26	8: 9	42: 20			0.233	0.557	0.117
Age (year)	52.0 ±11.5 (52.0)	57.6 ±13.4 (57.0)	58.9±14.1 (60.5)	5.034	0.008	0.323	0.007	1.000

History of Hypertension Diabetes	 39 31	 8 5	 41 29			 0.866 0.264	 0.222 0.774	 0.151 0.200
White cell count (mm^3) Neutrophil (%) Lymphocyte (%) Platelet count(mm^3) ESR (mm/h)	13,395±5,668(13,500) 83.9±7.6 (85.1) 8.1±4.3 (7.1) 267,029±130,429 (246,0) 70.4±26.3 (65.4)	13,335±7,191 (11,800) 81.2±9.2 (82.8) 8.9±4.4 (7.3) 221,647±103,296 (201,0) 75.8±21.6 (81.0)	14,361±6,416 (13,450) 84.5±8.5 (86.5) 8.3±4.9 (7.2) 265,371±120,681 (237,0) 66.9±25.2 (62.1)	0.455 1.103 0.210 0.982 0.901	0.635 0.335 0.811 0.377 0.409	1.000 0.649 1.000 0.530 1.000	1.000 1.000 1.000 1.000 1.000	1.000 0.422 1.000 0.596 0.605
C-reactive protein <6mg/L >6mg/L	 1 69	 1 16	 0 62			0.355	0.496	0.215
D-dimer <0.4µg/mL >0.4µg/mL	 32 38	 8 9	 22 40			0.921	0.233	0.384

The results are expressed as frequencies, percentages, and mean ± SD (median). P-value was calculated by using one-way ANOVA with *post hoc* Bonferroni test for continuous data and Fisher-Chi squared exact probability test for categorized data. P1= comparison between Group I and II, P2: comparison between Group II and III, and P3: Comparison between Group II and III.

Group I: Health care treatment, Group II: Remdesivir-treatment, Group III: Favipiravir-treatment, ESR: erythrocyte sedimentation rate

Table 3: Hematological Indices

Determinants	Group I (n=70)	Group II (n=17)	Group III (n=62)	One-way ANOVA		*Post hoc Bonferoni*		
				F-value	p-value	P1	P2	P3
Red cell count $\times 10^6/mm^3$	4.675±0.723	4.815±0.442	4.723±0.684	0.305	0.737	1.000	1.000	1.000
Hemoglobin (g/dl)	12.94±2.1	13.1±1.8	13.3±1.5	0.632	0.533	1.000	0.789	1.000
Hematocrit (%)	38.9±6.5	39.1±7.5	40.2±5.1	0.796	0.453	1.000	0.667	1.000
Mean cell volume (fL)	83.6±6.8	83.6±28.5	85.6±7.2	1.378	0.255	1.000	0.352	0.920
MCH (pg)	27.9±2.3	27.3±2.8	28.4±2.4	1.517	0.223	1.000	0.747	0.325
MCHC (g/dl)	33.4±1.7	32.7±1.0	33.1±1.3	1.578	0.210	0.249	1.000	0.712
RDW (CV)	13.3±1.3	13.1±0.7	13.2±1.1	0.507	0.603	1.000	1.000	1.000
Mentzer index	18.5±4.3	17.5±2.7	18.5±3.5	0.516	0.598	1.000	1.000	0.968
Shine and Lal index	1980.8±432.3	2301.8±424.7	2440.3±391.4	**20.636**	**<0.001**	**0.015**	**<0.001**	**0.673**
England and Fraser index	-44.93±10.5	-103.1±58.0	10.9±10.5	**224.6**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Sirvastata index	6.2±1.5	5.7±0.8	6.1±1.1	0.900	0.409	0.595	1.000	0.645
Green and King index	74.4±21.5	70.6±12.5	73.6±15.2	0.309	0.735	1.000	1.000	1.000
Red distribution width index	246.8±70.0	229.8±37.6	243.4±47.6	0.584	0.559	0.845	1.000	1.000
Ricerca index	3.0±0.8	2.8±0.3	2.8±0.4	1.094	0.338	0.665	0.745	1.000
Mean density of hemoglobin/liter-index	1.6±0.2	1.6±0.2	1.6±0.2	0.042	0.959	1.000	1.000	1.000
Mean cell hemoglobin density-index	0.33±0.02	0.33±0.01	0.33±0.01	1.577	0.210	0.246	1.000	0.686
Sirdah	40.1±8.2	39.4±6.8	40.9±8.6	0.313	0.732	1.000	1.000	1.000
Ehsani	36.9±10.4	35.4±9.8	38.3±11.9	0.590	0.556	1.000	1.000	0.992

The results are expressed as mean ±SD. P-value was calculated by using One-way analysis of variance (ANOVA) with *post hoc* Bonferroni test. P1= comparison between Group I and II, P2: comparison between Group II and III, and P3: Comparison between Group II and III. Group I: Health care treatment, Group II: Remdesivir-treatment, Group III: Favipiravir-treatment.

Table 4: Distribution of Cases According to the Category of Absolute Iron Deficiency (AID) and Restrictive Iron Deficiency (RID)

Red cell derived indexes	Group I (n=70)		Group II (n=17)		Group III (n=62)		P1	P2	P3
	RID	AID	RID	AID	RID	AID			
Mentzer index	2	68	0	17	2	60	1.000	1.000	1.000
Shine and Lal index	8	62	2	15	1	61	1.000	**0.036**	0.115
England and Fraser index	70	0	16	1	6	56	0.195	**<0.001**	**<0.001**
Sirvastata index	0	70	0	17	2	60	1.000	0.219	1.000
Green and King index	21	49	8	9	19	43	0.251	1.000	0.253
Red distribution width index	23	47	9	8	19	43	0.163	0.853	0.151
Ricerca index	67	3	17	0	62	0	1.000	0.247	1.000
Mean density of hemoglobin/liter-index	27	43	7	10	24	38	1.000	1.000	1.000
Mean cell hemoglobin density-index	66	4	17	0	61	1	0.582	0.370	1.000
Sirdah	3	67	0	17	3	59	1.000	1.000	1.000
Ehsani	2	68	0	17	2	60			
Total	289	481	76	111	201	481	0.432	**0.001**	**0.004**
Percentage	37.5	62.5	40.6	59.4	29.5	70.5			

The results are expressed as frequencies. P-value was calculated by using Fisher exact-Chi-Square test. P1= comparison between Group I and II, P2: comparison between Group II and III, and P3: Comparison between Group II and III.

Group I: Health care treatment, Group II: Remdesivir-treatment, Group III: Favipiravir-treatment.

Table 5: Distribution of Cases According to the Category of Absolute Iron Deficiency (AID) and Restrictive Iron Deficiency (RID)

Red cell derived indexes	Group 1 (n=70)				Group 1I (n=17)				Group 1I (n=62)			
	<0.4µg/mL		>0.4µg/mL		<0.4µg/mL		>0.4µg/mL		<0.4µg/mL		>0.4µg/mL	
	RID	AID	RID	AID	RID	AID	RID	AID	RID	AID	RID	AID
Mentzer index	2	30	0	38	8	0	9	0	2	20	0	40
Shine and Lal index	8	24	0	38	2	6	0	9	1	21	0	40
England and Fraser index	32	0	38	0	8	0	8	1	2	20	4	36
Sirvastata index	0	32	0	38	0	8	0	9	2	20	0	40
Green and King index	12	20	9	29	4	4	4	5	10	12	9	31
Red distribution width index	12	20	11	27	5	3	4	5	10	12	9	31
Ricerca index	30	2	37	1	8	0	9	0	22	0	40	0
Mean density of hemoglobin/liter-index	18	14	9	29	5	3	5	4	11	11	12	28
Mean cell hemoglobin density-index	30	2	36	2	8	0	9	0	22	0	40	0
Sirdah	2	30	1	37	0	8	0	9	2	20	1	39
Ehsani	2	30	0	38	0	8	0	9	2	20	0	40
Total	148	204	141	277	48	40	48	51	86	156	115	325
Percentage	42.0	58.0	33.7	66.3	54.5	45.5	48.5	51.5	35.5	64.5	26.1	73.9
p-value	**0.017**				0.408				**0.01**			

The results are expressed as frequencies. P-value was calculated by using Fisher exact-Chi-Square test.

Group I: Health care treatment, Group II: Remdesivir-treatment, Group III: Favipiravir-treatment.

Discussion

The results of this study showed that COVID-19 patients have a picture of mixed absolute and restrictive iron deficiency despite the values of hemoglobin and hematocrit are within the reference normal range. Favipiravir significantly reduced the percentage of restrictive iron deficiency compared with health care management with or without remdesivir. The mean value of hemoglobin of our patients is within the normal range. One meta-analysis included 17 articles that showed low hemoglobin level is a feature of

severe COVID-19, and it is not a laboratory feature of non-severe COVID-19.[24] Therefore, hypoxemia at the beginning of COVID-19 illness is a cause of preservation of stable hemoglobin levels.[25] The mean values of RDW in all COVID-19 groups are within the normal reference value of 11.6-14.6%, indicating that our patients are free from a poor prognosis.[26] The mean values of MCV are within the lower normal limits of both sexes (80-100fL). This indicated the red cell iron is decreased either due to absolute or restrictive iron deficiency. Dysregulation of iron metabolism is a feature of COVID-19 illness, and this explains that the iron deficiency could be absolute or the iron is not utilized by the red cell, in addition to the negative impact of inflammation on the status of iron. [27]

In this study, we used different indexes with different cutoff values that indicate evidence of absolute or restrictive iron deficiency. Our results showed variability in the mean values and discrimination status between absolute and restrictive iron deficiency. The significant changes in the Shine and Lal index indicate that Group II and III patients have absolute iron deficiency, while the mean ± SD of England and Fraser index indicates a significant restrictive iron deficiency in Groups I and II, while Group III showed absolute iron deficiency. Therefore summation of all indices can give a clear picture of the red cell indexes. Our results showed that COVID-19 patients managed with health care showed mixed absolute and restrictive iron of 59% and 41%, respectively. Hyperferritinemia resulted from inflammation played a role in the disturbances of iron metabolism in CODI-19 and is a significant marker of the pathogenesis or progression of COVID-19.[28] Our results agreed with another study that showed the serum iron is increased after few days of admission compared with the baseline values, indicating that there is a defect in the iron metabolism.[29] Therefore, some authors believe in the use of iron chelators in the management of COVID-19 as they eliminate the toxic effect of iron, and they have antiviral and antifibrotic effects.[30] The percentages of patients distributed into absolute and iron deficiency in a remdesivir-treated group have non-significantly differed from those without remdesivir-treatment. There is no evidence that remdesivir exerts an effect on the iron homeostasis in the management of COVID-19.[31] Favipiravir-treated patients showed a significantly lower percentage of patients with restrictive iron deficiency, indicating that favipiravir improves the utilization of iron by tissue, and seems to have an iron-chelator property. This observation confirmed the previous studies that favipiravir significantly benefits COVID-19 patients in terms of clearance the coronavirus and decreasing the progression of the disease.[32,33] The favorable effect of favipiravir on the restrictive iron deficiency was observed when the D-dimer level is >0.4µg/mL, a lower percentage was observed in patients with D-dimer >0.4µg/mL compared with <0.4µg/mL (26.1% versus 35.5%).

Conclusion

According to the results of this study, favipiravir improves the iron utilization by tissues by the evidence of reducing the percentage of restrictive iron deficiency. Further study is recommended to show the changes in the free serum iron level in patients treated with favipiravir with and without iron-chelating agents.

Limitations

As a peer our knowledge, this study highlights the beneficial effect of favipiravir via its effect on the red cell indices. One of the important limitations of the study is the small size of patients who are treated with remdesivir therapy which is unavoidable because this medicine is not always available in the medical centers, and the physician hardly used it in the guidelines of COVD-19.

Further perspectives

We believe that antiviral agents show pleiotropic effects against several elements in the body. Therefore, it will be beneficial to study the effects of favipirafir against the mediators of inflammation and lung fibrosis.

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References

[1] **Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB** et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020**;95**:E131-4.

[2] **Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW** et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;**323**:2052-9.

[3] **Chen T, Wu D, Chen H, Yan W, Yang D, Chen G**, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020; **368**: m1091.

[4] **Bennett TD, Hayward KN, Farris RW, Ringold S, Wallace CA, Brogan TV**. Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatr Crit Care Med. 2011;**12**:e233-6.

[5] **Liu Z, Sun R, Li J, Cheng W, Li L**. Relations of anemia with the all-cause mortality and cardiovascular mortality in general population: A meta-analysis. Am J Med Sci. 2019;**358**:191-9..

[6] **Kernan KF, Carcillo JA**. Hyperferritinemia and inflammation. Int Immunol. 2017; **29**:401-9.

[7] **Wessling-Resnick M**. Crossing the iron gate: Why and how transferrin receptors mediate viral entry. Annu Rev Nutr. 2018;**38**:431-58.

[8] **Lamb YN**. Remdesivir: First Approval. Drugs. 2020;**80**:1355-63.

[9] **Brown AJ, Won JJ, Graham RL, Dinnon KH 3rd, Sims AC, Feng JY**, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res. 2019; **169**: 104541.

[10] **de Wit E, Feldmann F, Cronin J, Jordan R, Okumura A, Thomas T**, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020;**117**:6771-6.

[11] **Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J**, et al. Favipiravir versus arbidol for COVID-19: A randomized clinical

trial. medRxiv. 2020; Advance online publication doi:10.1101/2020.03.17.20037432

[12] **Delang L, Abdelnabi R, Neyts J**. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res. 2018;**153**:85-94.

[13] **Shiraki K, Daikoku T**. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;**209**:107512.

[14] **Mentzer WC Jr**. Differentiation of iron deficiency from thalassaemia trait. Lancet. 1973;**1**:882..

[15] **Shine I, Lal S**. A strategy to detect beta-thalassaemia minor. Lancet. 1977;**1**:692-4.

[16] **England JM, Fraser PM**. Differentiation of iron deficiency from thalassaemia trait by routine blood-count. Lancet. 1973;**1**:449-52.

[17] **Srivastava PC**. Differentiation of thalassaemia minor from iron deficiency. Lancet. 1973;**2**:154-5.

[18] **Green R, King R**. A new red cell discriminant incorporating volume dispersion for differentiating iron deficiency anemia from thalassemia minor. Blood Cells. 1989;**15**:481-91; discussion 492-5.

[19] **Ricerca BM, Storti S, d'Onofrio G, Mancini S, Vittori M, Campisi S**, et al. Differentiation of iron deficiency from thalassaemia trait: a new approach. Haematologica. 1987;**72**:409-13.

[20] **Sirdah M, Tarazi I, Al Najjar E, Al Haddad R**. Evaluation of the diagnostic reliability of different RBC indices and formulas in the differentiation of the beta-thalassaemia minor from iron deficiency in Palestinian population. Int J Lab Hematol. 2008;**30**:324-30.

[21] **Ehsani MA, Shahgholi E, Rahiminejad MS, Seighali F, Rashidi A**. A new index for discrimination between iron deficiency anemia and beta-thalassemia minor: results in 284 patients. Pak J Biol Sci. 2009;**12**(5):473-5.

[22] **Telmissani OA, Khalil S, George TR**. Mean density of hemoglobin per liter of blood: a new hematologic parameter with an inherent discriminant function. Laboratory Haematology. 1999;**5**:149–52.

[23] **Tong L, Kauer J, Wachsmann-Hogiu S, Chu K, Dou H, Smith ZJ**. A new red cell index and portable RBC analyzer for screening of iron deficiency and Thalassemia minor in a Chinese population. Sci Rep. 2017;**7**:10510.

[24] **Ghahramani S, Tabrizi R, Lankarani KB, Kashani SMA, Rezaei S, Zeidi N**, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. 2020;**25**:30.

[25] **Setia R, Dogra M, Handoo A, Yadav R, Thangavel GP, Rahman AE**. Use of face mask by blood donors during the COVID-19 pandemic: Impact on donor hemoglobin concentration: A bane or a boon. Transfus Apher Sci. 2021:103160.

[26] **Foy BH, Carlson JCT, Reinertsen E, Padros I Valls R, Pallares Lopez R, Palanques-Tost E**, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Netw Open. 2020; **3**:e2022058.

[27] **Cavezzi A, Troiani E, Corrao S**. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. A narrative review. Clin Pract. 2020; **10**:1271.

[28] **Edeas M, Saleh J, Peyssonnaux C**. Iron: Innocent bystander or vicious culprit in COVID-19 pathogenesis? Int J Infect Dis. 2020; 97:303-5.

[29] **Bolondi G, Russo E, Gamberini E, Circelli A, Meca MCC, Brogi E,** et al. Iron metabolism and lymphocyte characterisation during Covid-19 infection in ICU patients: an observational cohort study. World J Emerg Surg. 2020;**15**:41.

[30] **Perricone C, Bartoloni E, Bursi R, Cafaro G, Guidelli GM, Shoenfeld Y**, et al. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. Immunol Res. 2020;**68**:213-24.

[31] **Chang R, Ng TB, Sun WZ**. Lactoferrin as potential preventative and adjunct treatment for COVID-19. Int J Antimicrob Agents. 2020;**56:**106118.

[32] **Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J,** et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (Beijing). 2020;**6**:1192-8.

[33] **Ghasemnejad-Berenji M, Pashapour S**. Favipiravir and COVID-19: A Simplified Summary. Drug Res (Stuttg). 2021;**71**:166-70.