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CORRESPONDENCE

Hematologic parameters in patients with COVID-19 infection

To the Editor:

A cluster of unexplained pneumonia cases was reported by the People's Republic of China to the World Health Organization (WHO) on 31 December, 2019. The etiology for this outbreak was a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was responsible for the Corona Virus Disease 2019 (COVID-19).[1] Singapore confirmed its first imported case on 23 January 2020 and local transmission was detected on 4 February, 2020. As of 28 February, 2020, Singapore had 96 confirmed cases of COVID-19 infection. SARS-CoV-2 was confirmed by real time reverse transcriptase-polymerase chain reaction (RT-PCR), performed on respiratory samples of these patients. A majority of 69 out of these 96 patients were treated at the National Centre for Infectious Diseases (NCID). We herein present a detailed analysis of the hematological parameters of the COVID-19 patients at the NCID (see Table 1).

Of the 69 patients that had been admitted to the NCID, 26 patients were still hospitalized, and 43 patients had been discharged as of 28 February 2020. Also, 67 patients had at least one complete blood count (CBC) performed during inpatient stay; 65 patients had CBC performed on day of admission. We analyzed the hematological indices of all COVID-19 infected patients from day 1 of admission until 28 February 2020. We obtained data from the Laboratory Information System (LIS) exclusively which provided information on the age, gender, ethnicity and location of each patient. We divided the patients into two groups; ICU and non-ICU patients. Additionally, flow cytometry on lymphocyte subsets was performed from 24 to 28 February 2020, on a subgroup of nine COVID-19 patients; five ICU patients and four non-ICU patients (with six normal individual blood samples as controls). Immunophenotyping was performed using a Becton Dickinson FACSCanto II Flow analyzer.

Most patients were of Chinese ethnicity (89.5%), while the minority were of Malay (4.5%), Indian (1.5%) and other ethnicities (4.5%). Just 9 out of the 67 (13.4%) patients required ICU care. Notably, ICU patients were about a decade older than the non-ICU patients; the median age of ICU patients was 54 years old while the median age of non-ICU patients was 42 years old (P = .02). On admission, leukopenia was observed in 19 patients (29.2%) with only one patient presenting with severe leukopenia (WBC < 2×10^9/L). Lymphopenia featured in 24 patients (36.9%) with 19 having moderate lymphopenia (absolute lymphocyte count [ALC] 0.5-1 $\times 10^9$/L), and five with severe lymphopenia (ALC < 0.5×10^9/L). Most patients had normal platelet counts, with 13 patients (20.0%) having mild thrombocytopenia (platelet count 100-150 $\times 10^9$/L).

Peripheral blood film review showed that a higher number of patients (69%) who were lymphopenic had the presence of a few reactive lymphocytes, of which a subset appeared lymphoplasmacytoid. This contrasts with the severe acute respiratory syndrome (SARS) outbreak in 2003 where reactive lymphocytes were not observed in a study on Haematologic parameters in SARS in Singapore[2] and only in 15.2% of cases in a similar Hong Kong study.[3]

Our analysis revealed that on admission, most patients had a normal CBC (normal Hb, WBC and platelet count) and lactate dehydrogenase (LDH). And, no patient presented with moderate or severe thrombocytopenia that is frequently observed in other viral illnesses such as dengue fever which is endemic in our region.

However, 28% of all patients presented with lymphopenia (ALC < 1×10^9/L). This number is significantly smaller compared to 63% of patients in Wuhan, China, and 42% of patients outside of Wuhan who presented with lymphopenia.[4,5] This disparity in numbers may in part be reflective of the extent of epidemiological data available within the surveillance pyramid in those regions. Those requiring ICU care had a lower ALC and higher LDH. These were findings also reported by Huang et al on the characteristics of COVID-19 patients in Wuhan, China.[4] Lymphopenia has been well described in retrospective analysis of patients in Hong Kong and Singapore afflicted with SARS-CoV in 2003, and was associated with adverse outcomes and ICU stay.[2,3,6] Lymphopenia featured prominently in our COVID-19 ICU group with a median nadir ALC of 0.4×10^9/L, compared to 1.2×10^9/L in the non-ICU group. Monitoring of such hematologic parameters may help to identify patients who may need ICU care. An ALC approaching severe lymphopenia of <0.6×10^9/L may possibly be considered as one of the indicators for early admission for supportive care in the ICU.

Between the ICU (n = 9) and non-ICU (n = 58) patients, using Fisher's exact tests, we found that admission ALC and LDH stood out as discriminating laboratory indices with a P value of <.001 and .005 respectively. The ICU patients in general presented with more profound lymphopenia with seven out of nine being lymphopenic; four of whom had severe lymphopenia. Note, LDH was performed for 4 out of the 9 ICU patients on admission, and all four cases had a raised LDH with a median value of 1684 U/L (reference range 270-550 U/L). Comparatively non-ICU patients tend to present with a normal LDH, median value 401 U/L; with only five out of 26 non-ICU patients presenting with a raised LDH above 550 U/L. During their stay in ICU, those patients developed more profound, statistically significant decrements in their hemoglobin levels, with ALC and absolute monocyte count (AMC) levels compared to the non-ICU group. The median nadir ALC was 0.4×10^9/L in the ICU group compared to 1.2×10^9/L in the non-ICU group (P value <.001), while the median nadir AMC was 0.2×10^9/L in the ICU group, compared to 0.4×10^9/L in the non-ICU group (P value <.001).

TABLE 1 Comparisons of demographic and haematologic parameters between ICU and non-ICU patients

		Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
		Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Demographic characteristics at admission	**Age (years)**	41 (32-53)		54 (47-62)		.02	42 (35-54)	
	Ethnicity					.65		
	Chinese		52 (89.7)		8 (88.9)			60 (89.6)
	Malays		3 (5.2)		0 (0.0)			3 (4.5)
	Indians		1 (1.7)		0 (0.0)			1 (1.5)
	Others		2 (3.5)		1 (11.1)			3 (4.5)
	Gender					.72		
	Males		31 (53.5)		6 (66.7)			37 (55.2)
	Females		27 (48.6)		3 (33.3)			30 (44.8)
Blood profile at admission	**Hb (g/dL)**[a]	14.2 (12.9 - 15.2)		13.2 (12.5-14)		.07	14 (12.9-15.2)	
	WBC ($\times 10^9$/L)[a]	4.7 (4.0 - 5.8)		5.1 (3.5-8.2)		.87	4.7 (3.9-5.8)	
	WBC ($\times 10^9$/L)[a]					.36		
	<2		1 (1.8)		0 (0.0)			1 (1.5)
	2-4		14 (25.0)		4 (44.4)			18 (27.7)
	>4		41 (73.2)		5 (55.6)			46 (70.8)
	ALC ($\times 10^9$/L)[a]	1.3 (0.9 - 1.7)		0.5 (0.48-0.8)		.0002	1.2 (0.8-1.6)	
	ALC ($\times 10^9$/L)[a]					<.001		
	<0.5		1 (1.8)		4 (44.4)			5 (7.7)
	0.5-1.0		16 (28.6)		3 (33.3)			19 (29.2)
	>1		39 (69.6)		2 (22.2)			41 (63.1)
	AMC ($\times 10^9$/L)[a]	0.5 (0.4 - 0.6)		0.3 (0.2-0.5)		.12	0.5 (0.3-0.6)	
	AMC ($\times 10^9$/L)[a]					.19		
	≤0.3		11 (19.6)		4 (44.4)			15 (23.1)
	>0.3		45 (80.4)		5 (55.6)			50 (76.9)
	ANC ($\times 10^9$/L)[a]	2.6 (2.1 - 3.8)		4.2 (2.1-6.9)		.17	2.6 (2.1-4.1)	
	ANC ($\times 10^9$/L)[a]					.99		
	<0.5		0 (0.0)		0 (0.0)			0 (0.0)
	0.5-1.0		2 (3.6)		0 (0.0)			2 (3.1)
	>1		54 (96.4)		9 (100.0)			63 (96.9)
	Platelets ($\times 10^9$/L)[a]	201 (157-263)		217 (154-301)		.81	201 (155-263)	
	Platelets ($\times 10^9$/L)[a]					.67		
	<100		0 (0.0)		0 (0.0)			0 (0.0)
	100-150		12 (21.4)		1 (11.1)			13 (20.0)
	>150		44 (78.6)		8 (88.9)			52 (80.0)
	LDH (U/L)[b]	401 (352-513)		1684 (1053-2051)		.003	446 (364-595)	
	LDH (U/L)[b]					.005		
	≤550		21 (80.8)		0 (0.0)			21 (70.0)
	>550		5 (19.2)		4 (100.0)			9 (30.0)
Blood profile during Inpatient stay	**Nadir Hb (g/dL)**	13.6 (12.7-15.1)		11.1 (10.2-11.9)		<.001	13.3 (12.2-15)	
	Nadir ALC ($\times 10^9$/L)	1.2 (0.8-1.6)		0.4 (0.3-0.5)		<.001	1.0 (0.8-1.5)	
	Nadir ALC ($\times 10^9$/L)					<.001		
	<0.5		1 (1.7)		7 (77.8)			8 (11.9)
	0.5-1.0		23 (39.7)		2 (22.2)			25 (37.3)
	>1		34 (58.6)		0 (0.0)			34 (50.8)
	Nadir AMC ($\times 10^9$/L)	0.4 (0.3-0.5)		0.2 (0.19-0.23)		<.001	0.4 (0.3-0.5)	

(Continues)

TABLE 1 (Continued)

	Non-ICU patients (n = 58)		ICU patients (n = 9)			Overall (n = 67)	
	Median (IQR)	No. (%)	Median (IQR)	No. (%)	*P* value	Median (IQR)	No. (%)
Nadir AMC ($\times 10^9$/L)					<.001		
≤0.3		14 (24.1)		8 (88.9)			22 (32.8)
>0.3		44 (75.9)		1 (11.1)			45 (67.2)
Nadir Platelets ($\times 10^9$/L)	192 (150-261)		154 (131-216)		.15	185 (148-259)	
Nadir Platelets ($\times 10^9$/L)					.69		
<100		0 (0.0)		0 (0.0)			0 (0.0)
100-150		15 (25.9)		3 (33.3)			18 (26.9)
>150		43 (74.1)		6 (66.7)			49 (73.1)
Peak ANC ($\times 10^9$/L)	3.5 (2.6-4.4)		11.6 (9.3-13.8)		<.001	3.8 (2.7-5.0)	
Peak ANC ($\times 10^9$/L)							
<0.5		0 (0.0)		0 (0.0)			0 (0.0)
0.5-1.0		0 (0.0)		0 (0.0)			0 (0.0)
>1		58 (100.0)		9 (100.0)			67 (100.0)
Peak LDH (U/L)[c]	451 (367-629)		1081 (752-1460)		<.001	470 (386-684)	
Peak LDH (U/L)[c]							
≤550		35 (66.0)		0 (0.0)	<.001		35 (56.5)
>550		18 (34.0)		9 (100.0)			27 (43.6)

Note: (a) Data includes Singapore residents and foreigners. Foreigners have been included as "Others" under ethnicity. (b) For continuous variables, median and IQR (Interquartile range) have been presented due to the non-normality of the data. Correspondingly, Mann-Whitney tests were used to assess if differences between ICU and non-ICU groups were statistically significant. (c) For categorical variables, Fisher's exact tests were used to check if there is any association between the ICU and non-ICU groups due to the small expected cell counts when blood profiles were categorized. (d) Nadir and peak of the hematologic parameters are obtained by following up with the patients from the point of admission to their latest available blood test value as at 28 February 2020.

Abbreviations: ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; Hb, Hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cell.

[a]In total, 69 patients were admitted to NCID. And, 67 patients had at least one complete blood count (CBC) performed during inpatient stay; 65 patients had CBC performed on day of admission.

[b]There were 30 patients who had LDH (reference range 270-550 U/L) performed at admission.

[c]There were 62 patients who had LDH (reference range 270-550 U/L) performed during inpatient stay.

Notably, ICU patients tend to develop neutrophilia during the hospitalization with a median peak Absolute Neutrophil Count (ANC) of 11.6 $\times$ 10^9/L, compared to 3.5 $\times$ 10^9/L in the non-ICU group (*P* value < .001). The ICU group also had a peak LDH which was significantly higher than the non-ICU group. The median nadir platelet count remained in the normal range (above 150 $\times$ 10^9/L) for both groups and was not a discriminating test on admission or during the hospitalization. To date, three out of the nine ICU patients have been discharged from ICU care. We noted increasing values in their WBC, ALC, AMC, and down trending LDH as their clinical condition improved. Flow cytometry performed on peripheral blood lymphocytes demonstrate prominent lymphopenia in the ICU patients as compared to the non-ICU patients and normal controls. The ICU patients have significantly lower CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts. The CD4/CD8 ratio was not inverted in all groups of patients, unlike other viral infections such as human immunodeficiency virus (HIV) and cytomegalovirus (CMV) infections where the CD4/8 ratio is usually inverted.

The limitation of our study is missing data as laboratory investigations were not performed daily on all patients especially those who were minimally symptomatic in the general isolation ward. We also recognize that correlating onset of symptoms (days of illness) with hematological parameters is important and would require a case note review which was not done in this study. However, this review is a reflection of real-life clinical setting wherein a proportion of asymptomatic patients (admitted from positive RT-PCR results during contact tracing) may not have significant anomalies on their CBC at presentation. Lastly, admission laboratory results for ICU patients transferred from other institutions were not reflected in our data set. This may result in lower hematological indices on admission as those patients were already in critical condition. Further studies should be conducted comparing patients' onset of symptoms and correlating their clinical condition to laboratory findings.

In conclusion, our study showed that on admission, older age, lymphopenia and raised LDH were associated with ICU admissions. Patients who were transferred to the ICU had a deeper nadir ALC,

nadir AMC and nadir hemoglobin, and higher peak ANC and peak LDH levels as compared to patients who did not require ICU stay.

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CONFLICT OF INTEREST

All authors declare no competing interests.

This study was approved by the National Healthcare Group Domain Specific Review Board (DSRB). No patient identifiers were collected and approval of exemption for informed consent was obtained.

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REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *New Engl J Med*. 2020;382:727-733.
2. Chng WJ, Lai HC, Earnest A, Kuperan P. Haematological parameters in severe acute respiratory syndrome. *Clin Lab Haematol*. 2005;27:15-20.
3. Lee N, Hui DS, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 2003;348:1986-1994.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
5. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*. 2020;368:m606.
6. Wong RSM, Wu A, To KF, et al. Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ*. 2003;326:1358-1362.