Dynamic Changes in Routine Laboratory Parameters with COVID-19: In-depth Analysis of 17 Patients Requiring Critical Care

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***Abstract*—Dynamic changes in routine blood parameters in COVID-19 patients might be helpful to prognosticate deterioration in COVID-19 patients and evaluate treatment effect. Our study aimed to evaluate the temporal changes in red blood cell indices (MCV, MCH, MCHC, RDW) in COVID-19 patients and the association of other relevant clinical parameters. We analysed 17 medical records of COVID-19 patients in retrospect who required critical care from 1 January 2020 until 28 February 2021 in Hospital Tuanku Fauziah, Perlis, Malaysia. Data extracted include details with regards to escalation and de-escalation of oxygen therapy, clinical and laboratory parameters. There were three time points of interest in our study: (i) admission (Adm), (ii) highest mode of oxygen therapy (HighM), and (iii) weaned off oxygen therapy (WeanOxy). The result showed that the mean duration to clinical deterioration requiring the highest mode of oxygen delivery was 2.3 ±1.85 days and the highest escalation device for oxygen delivery was high flow nasal cannula (n=7, 41.2%). There was no statistically significant difference in RDW, MCV, MCH, and MCHC at different clinical time points, $p>0.05$. However, there was a statistically significant increment in TWBC trend between Adm-HighM-WeanOxy, $\chi 2(2)=7.023$, $p=0.030$. Our study did not find evidence of structural RBC changes reflected in RBC indices. However, recovery from COVID-19 was reflected in the rise of TWBC and ANC, similar to that observed with other viral illnesses.**

***Index Terms*—clinical deterioration, COVID-19, critical care, leukocyte count, Malaysia, SARS-CoV-2**

I. Introduction

The global impact of COVID-19 was profound. The disease and healthcare burden of COVID-19 is continually expanding as the disease spread between people [1], particularly in COVID-19 hotspots.

COVID-19 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. It belongs to β-coronavirus genera with single strain RNA [2]. The virus has Open Reading Frames (ORFs) that consists of Spikes (S), Membranes (M), Envelopes (E), and Nucleocapsids (N) with the S parts being a glycoprotein capable to attach to host cells' receptors. COVID-19 has also been discovered to survive in host B and T cells, at the same time activating cascade of cytokine-chemokine reaction and secretion ('cytokine storm'), contributing to the clinical presentation of Acute Respiratory Distress Syndrome (ARDS) [3].

Various molecular pathogeneses of SARS-CoV-2 in COVID-19 pneumonia and ARDS have been delineated in literatures thus far. One such example is with regards to COVID-19 effects on the Red Blood Cells (RBCs). It was suggested that RBCs from COVID-19 patients may be less responsive to environmental milieu when traveling from the lungs to peripheral capillaries and vice versa. This is evident clinically as ventilation/perfusion mismatch commonly observed in COVID-19 patients [4].

Studies have also suggested disruption in RBC structural membrane and homeostasis at the protein and lipid levels [4]. Apart from that, elevated Red cell Distribution Width (RDW) in hospitalized COVID-19 patients has been associated with a significantly increased risk of mortality and septic shock [5].

COVID-19 patients were also at risk of hypercoagulable state with increased risk of thromboembolic phenomenon, particularly in critically ill patients [6].

The aforementioned literatures highlighted the dynamic changes in routine blood panels among COVID-19 patients. Therefore, these parameters might be helpful in the clinical prognosis among COVID-19 patients and the evaluation of the treatment effect [7].

However, studies on the 2019 novel coronavirus disease (COVID-19) have generally been limited to epidemiologic studies and clinical characteristics and management, with little emphasis on detailed evaluation of laboratory changes in clinically deteriorating COVID-19 patients. Therefore, our study aimed to remedy this by investigating the temporal changes and progression of clinical and laboratory markers in a subset of COVID-19 patients requiring critical care in our study centre.

II. Methods

This retrospective study involved data transcription and analyses from inpatient medical records of patients

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diagnosed with Stage IV and Stage V COVID-19 from Hospital Tuanku Fauziah, Perlis, Malaysia from 1 March 2020 until 28 February 2021. Hospital Tuanku Fauziah (HTF) is a designated COVID-19 hybrid hospital catering for the population of 255,000 people in the state of Perlis, situated in northwest Peninsular Malaysia.

Personal identifiers of eligible patients were traced from the admission log in the Department of Anesthesiology and Critical Care of HTF. Individual medical record thence was traced from the record office.

Data were collected at specific time points of interest. These time-points of interest includes:

- *Adm* referring to the time point at admission
- *HighM* referring to the time point of highest mode of oxygen therapy
- *WeanOxy* referring to the time point of weaning off oxygen therapy

Extracted data include the clinical characteristics and progression (i.e. presenting sign and symptoms, mode of oxygen therapy and oxygen titration), laboratory parameters (i.e. parameters in arterial blood gas including the saturation of arterial oxygen (SaO_2), red blood cell indices: Haemoglobin (Hb), Haematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Cell Distribution width (RDW), other routine blood panel: Total White Blood Cell (TWBC) and differential counts, Platelet (Plt), C-Reactive Protein (CRP), Creatinine, D-dimer, and alanine aminotransferase (ALT)) and vital signs (i.e. Mean Arterial Pressure (MAP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), heart rate, and respiratory rate).

Data extraction was performed by trained abstractors on separate data sheet(s).

A. Inclusion Criteria

All patients diagnosed with COVID-19 as confirmed with positive polymerase chain reaction (PCR) test, with Stage IV or Stage V COVID-19 at admission or during in-ward clinical progression.

B. Exclusion Criteria

COVID-19 patients with Stage I who was asymptomatic and monitored in local quarantine centre without clinical deterioration that requires transfer to tertiary care.

C. Ethical Approval

The study was registered with the National Medical Research Register of the Ministry of Health Malaysia (NMRR-21-205-58536) and received ethical clearance from the Medical Research and Ethics Committee (MREC) of the Ministry of Health Malaysia (KKM/NIHSEC/P21-370(4)).

D. Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Data normality were determined by Jarque-Bera test [8] whereby skewness of less than ± 1 and kurtosis of less than ± 3 signifies data that is normally distributed. Normally distributed numerical data were described in mean and standard deviation. Descriptive data such as gender and race were described using percentages and distribution.

Comparison of selected numerical variables in three continuous time-points were performed either using Repeated Measures analysis of variance (RM ANOVA) (i.e. MAP and heart rate), in normally distributed data, or Friedman test with Bonferroni correction (i.e. red cell indices including MCV, MCH, MCHC and RDW, white cell indices including TWBC, ANC and ALC), in skewed data.

III. Results

There was a total of 117 patients of various clinical staging admitted for COVID-19 in our centre during the study period. A total of 17 patients with clinical Stage IV and V COVID-19 at admission or during progression in the ward were included in this analysis.

The baseline sociodemographic and clinical characteristics of patients are depicted in Table I.

TABLE I. Baseline Socio-demographic and Characteristics (N=17)

Variable(s)	Mean ± SD	Frequency (%)
Age (in years)	57.2 ± 16.33	
Gender		
Male		9 (52.9)
Female		8 (47.1)
Presenting symptom(s)		
Fever		12 (70.6)
Cough		11 (64.7)
Anosmia		1 (5.9)
Ageusia		1 (5.9)
Shortness of breath		4 (23.5)
Asymptomatic		3 (17.6)
Past medical history		
HPT		8 (47.1)
Coronary heart disease		2 (11.8)
DM		7 (41.2)
COPD		0 (0.0)
BA		1 (5.9)
CVA		0 (0.0)
Mode of oxygen therapy on admission		
Room air		10 (58.8)
Nasal prong oxygen		5 (29.4)
Venturi mask		1 (5.9)
Face mask		1 (5.9)
Highest escalation device for oxygen delivery		
VM 40%		3 (17.6)
VM 60%		4 (23.5)
HFNC		7 (41.2)
Assisted ventilation		2 (11.8)
Nasal prong		1 (5.9)
Positive D-dimer		
Admission		3 (17.6)
Worse clinical		3 (17.6)
Off oxygen		0 (0.0)

Note: Abbreviation: BA: Bronchial asthma, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, DM: Diabetes mellitus, HFNC: High flow nasal cannula, HPT: Hypertension

The mean time duration from *Adm* to *HighM* was 2.3 ± 1.85 days whereas the mean time duration from *Adm* to *WeanOxy* was 9.3 ± 6.14 days.

With regards to vital signs, there was a significant difference in the mean MAP between *Adm* (μ=98.4 ± 11.16 mmHg) *vs. HighM* (μ=89.1 ± 10.87 mmHg) *vs. WeanOxy* (μ=92.4 ± 11.14 mmHg), *F*=5.053, *df*=2, *p*=0.015. Post-hoc pairwise analysis with Bonferroni correction showed significant reduction in MAP at *HighM vs. Adm* (p=0.002). Pairwise comparison between *Adm vs. HighM* time points revealed the median drop in SBP of 0.15% (Range: -0.63 to 0.58%), DBP of 0.03% (Range: -0.08% to 0.22%) and MAP of 0.08% (Range: -0.26% to 0.27%). Repeated measurement of the heart rate also showed clinical significance between the different time points, *F*=17.31, *df*=2, *p*<0.001 with significant reduction in HR was observed between *Adm. vs. HighM* (*p*=0.005) and between *Adm. vs. WeanOxy* (p=0.002).

There was also a strong correlation between PO_2 and SaO_2 even during the critical period of COVID-19 (at the time point of highest escalation of oxygen therapy), *r*=0.752, *p*=0.001.

There was a statistically significant difference in TWBC at different clinical condition, $\chi 2(2)=7.023$, *p*=0.030 (Table II).

TABLE II. REPEATED MEASUREMENT OF ROUTINE BLOOD PARAMETERS IN PATIENTS WITH CRITICAL COVID-19

Variable(s)	Continuous time point(s)			χ^2 *(df)*	*p*-value[a]
	Adm **Median (IQR)**	***HighM*** **Median (IQR)**	***WeanOxy*** **Median (IQR)**		
Red cell indices					
Hb	13.0 (3.10)	12.9 (2.80)	12.7 (2.60)	5.07 (2)	0.079
Hct	39.0 (6.00)	39.0 (6.00)	38.0 (6.00)	5.69 (2)	0.058
MCV	81.8 (3.90)	81.8 (3.90)	80.7 (4.00)	0.63 (2)	0.728
MCH	27.1 (2.90)	27.1 (2.90)	27.2 (3.60)	2.97 (2)	0.227
MCHC	33.8 (1.90)	33.8 (1.90)	33.5 (2.60)	0.05 (2)	0.975
RDW	13.5 (1.40)	13.5 (1.40)	13.7 (3.30)	1.25 (2)	0.535
White cell indices					
TWBC	6.89 (2.32)	6.69 (4.00)	12.7 (7.26)	7.02 (2)	0.030*
ANC	5.05 (2.31)	4.17 (2.79)	8.89 (6.47)	7.02 (2)	0.030*
ALC	1.54 (0.54)	1.17 (1.20)	1.22 (1.06)	0.98 (2)	0.614
Others					
Platelet	261.0 (124.00)	266.0 (124.00)	290.0 (109.00)	4.23 (2)	0.120

Note: [a]Friedman test with Bonferroni correction applied
*Statistically significant

Post-hoc analysis with Wilcoxon signed-rank tests conducted with a Bonferroni correction for TWBC showed a statistically significant increment in TWBC between *Adm vs. WeanOxy* (Z=-2.490, p=0.013). Similar trend was observed with ANC at different clinical condition, $\chi 2(2)=7.023$, p=0.030.

The post-hoc analysis with Wilcoxon signed-rank tests with Bonferroni correction showed a statistically significant increment in ANC between *Adm vs. WeanOxy* (*Z*=-2.667, *p*=0.008).

Otherwise, there were no significant differences in respiratory rate, CRP, ALT, fibrinogen and ferritin level between the readings between the time point of admission, worst clinical condition, and at the point of recovery.

IV. DISCUSSION

Our study found no change in red cell indices at different time points in the management of COVID-19 patients requiring critical care. This is in contrast to the finding from a prospective study of 49 COVID-19 patients, including 16 with severe illness that found significant association between elevated RDW and increased odds of severe COVID-19 [9] and predicts mortality [10]. Despite our negative finding, we did observe the increasing numerical trend of RDW during disease progression despite not reaching statistical significance, with the highest value still within normal limit.

Theoretically, RDW shows the difference in size between the smallest and the largest erythrocyte in the blood sample [11]. The normal range for RDW in an adult female is 12.2 to 16.1%, and between 11.8 to 14.5% in an adult male. A high RDW indicates anisocytosis, which may also signal iron, folate or B12 deficiency. However, interpretation of RDW alone may not be clinically accurate to suggest the underlying disorder. MCV, which measures the average volume of a red blood cell should be interpreted together to give a more comprehensive clinical picture of the root cause of clinical disruption.

Apart from that, we did find that the TWBC and ANC increased towards the recovery period, as similarly observed with other viral illnesses [12]. Recovery period is marked by the increment of these parameters as the bone marrow began to recover from myelosuppression that results from the initial infection [13], suppressing the myeloid lineage of cell production.

Our findings of the strong correlation between PO_2 and SaO_2 during the critical period of COVID-19 demonstrate the cooperative interaction between the Hb and oxygen molecules. The SaO_2 is the percentage of available binding sites present on the hemoglobin that will bind to oxygen in the arterial blood, while PO_2 is the driving pressure for oxygen molecules to enter and chemically bind with haemoglobin in the red blood cell [14].

Additionally, we did observe a progressive numerical increase in MCV, MCH, RDW and ALC, and a decrease in ANC up to a month following hospital discharged in a

subset of our patients (not part of the study analysis). However, the numerical values were still within normal limits and may not have direct clinical significance. Therefore, a prospective study looking at the variation in laboratory parameters in patients with COVID-19 following hospital discharge would aid our understanding on the changes in clinical parameters following clinical recovery from COVID-19.

Our study is limited by the number of patients available for analyses and the purposive sampling method. However, we did manage to retrieve credible dataset for preliminary analysis with regards to COVID-19 patients requiring critical care. For future studies, we would recommend bigger sample size and the presence of a control group for a more definitive conclusion when comparing COVID-19 to other viral pneumonia illnesses.

To the best of our knowledge, this is the first paper of its kind studying the temporal relationship of red cell indices with regards to clinical improvement and/or deterioration in COVID-19 patients.

V. Conclusion

Despite not showing statistical significance in changes of red cell indices in COVID-19 patients requiring critical care, we did observe the increasing trend of MCV, MCH and RDW in patients with severe and critical COVID-19. Our study demonstrated the increasing TWBC and ANC as hallmarks of clinical recovery in patients with COVID-19.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Karniza Khalid, Amira Aishah Che Ani, Azhar Abdul Orani, and Nur Najmi Abdul Halim conceptualized and conducted the research; Karniza Khalid analyzed and interpreted the data; Karniza Khalid, Amira Aishah Che Ani, Azhar Abdul Orani, and Nur Najmi Abdul Halim wrote the paper, Azman Abd Hamid provided critical review of the final draft; all authors had approved the final version.

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