ORIGINAL ARTICLE

Full Blood Count Parameters in COVID-19 Patients With Disease Severity, Patient Outcome and Vaccination Status

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ABSTRACT

Introduction: A link between full blood count (FBC) parameters with the severity and prognosis of individuals with coronavirus disease 2019 (COVID-19) infection is shown. We aim to identify changes in FBC parameters depending on patients' characteristics, the severity of the disease and vaccination status. **Methods:** A cross-sectional retrospective laboratory study is done on 208 respondents who were selected from February 2021 to December 2022 in the Pathology Department of the Tuanku Ja'afar Hospital in Negeri Sembilan. All patients are confirmed COVID-19 positive by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of pharyngeal and nasal swab specimens. Patients are further classified based on their COVID clinical stages, severity, vaccination status and outcome. The statistical data are analysed using IBM SPSS version 27. **Results:** Severe patients have significantly lower absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute eosinophil count (AEC) and absolute basophil count (ABC) but higher mean platelet volume (MPV), absolute neutrophil count (ANC), neutrophil to lymphocyte ratio (NLR) and immature granulocytes (IG) compared to non-severe patients ($p < 0.05$). Similar findings are seen among non-survivors ($p < 0.05$). Fully vaccinated patients have significantly lower NLR and MPV but higher ALC, AMC, AEC and ABC than unvaccinated or partially vaccinated patients ($p < 0.05$). **Conclusion:** Selected FBC parameters of COVID-19 patients (platelets, ANC, NLR, MPV, ALC, AMC, AEC, and ABC) are significantly different depending on patients' severity, outcome and vaccination status. These results might give a clear insight for clinicians to anticipate the severity and outcome of patients based on the patient's FBC parameters.
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INTRODUCTION

Since the initial report of COVID-19 in Wuhan, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread swiftly over the world resulting in a global health pandemic. Until October 2022, Malaysia had about 4.8 million cases and 38 thousand deaths (1). Most patients have a self-limiting illness however about 15% presented with a severe condition that could lead to multiple organ failure and death. The most prevalent cause of death was found to be septic shock and multi-organ failure, which were commonly caused by suppurative pulmonary infection.

Mortality rates are more pronounced in high-risk groups like the elderly and those having preexisting medical co-morbidity (2, 3, 4). Several drastic measures have been implemented across the world to reduce the risk of the COVID-19 pandemic transmission. Vaccination programs have been proven to lower COVID-19 mortality in Malaysia and other countries (5, 6).

Identification of those who have a mild or moderate disease that may progress to a critical illness is beneficial since it allows for earlier treatment to avoid deteriorating outcomes. Several studies have indicated that FBC indices like platelet counts, ALC, ANC and AMC appear to be linked to COVID-19's lethality and severity (2, 7, 8, 9). Thus, monitoring the FBC parameters has importance in detecting the disease progression as it is immediately available and routinely performed in almost all patients during hospitalisation. Though many research has been conducted, a few have examined the relationships between FBC characteristics and COVID-19 in the Malaysian population at the time this study was started. We aimed to profile the changes in FBC parameters in COVID-19 patients concerning their clinical presentation, the severity of the disease and an association with their vaccination status.

MATERIALS AND METHODS

Study population

A cross-sectional, retrospective study was conducted in the Pathology Department, Hospital Tuanku Ja'afar, Seremban, Negeri Sembilan from February 2021 to December 2022. A total of 208 patients were selected by systematic random selection from the list of COVID-19 patients. All patients were confirmed positive for the virus using real-time reverse transcriptase-polymerase chain reaction on pharyngeal and nasal swab specimens.

Patient data which include sociodemographic, clinical, laboratory, treatment, the severity of the disease and vaccination status were retrieved from the patient information system and recorded. Patients with incomplete data were eliminated.

Analytical method

The FBC test was performed by an automated haematological analyser, Sysmex XN-3000 (Sysmex, Kobe, Japan).

Patient classification

i) Patients were divided into two age groups, which were 18-59 years old and above 60 years old.

ii) The patients were clinically categorised into the 5 COVID-19 stages (CAT1-CAT5) according to "COVID-19 management guidelines in Malaysia"(10).

"CAT1: Asymptomatic"
"CAT2: Symptomatic without pneumonia"
"CAT3: Symptomatic with pneumonia, without the requirement for supplemental oxygen."
"CAT4: Symptomatic with pneumonia, requiring supplemental oxygen."
"CAT5: Critically ill with multi-organ involvement."

iii) Patients were further grouped by their severity and outcome on admission, where CAT4 and CAT5 were defined as severe cases while CAT1- CAT3 was defined as a non-severe group.

iv) For the patients' outcomes, those discharged home upon that admission were categorised as survivors, while patients who succumbed to COVID-19 were categorised as non-survivors.

v) For the vaccination status, patients who never received any COVID-19 vaccine were defined as unvaccinated, patients who received one dose of COVID-19 vaccine as partially vaccinated, and those with two doses of COVID-19 vaccine were grouped as completed vaccination.

Statistical analysis

IBM Statistical Package for the Social Sciences (SPSS) version 27 was used to perform statistical analysis on the data. For continuous variables, the data were expressed as median (interquartile range [IQR]) and for categorical variables, as the count (percentages). The association between demographic data and COVID-19 stages, severity, and outcome were analysed with Chi-square and Fisher's exact statistical test. FBC parameter differences in COVID-19 stages were analysed with Kruskal-Wallis statistical test while FBC parameter differences between severe vs non-severe, and survivor vs non-survivor were explored using the Mann-Whitney test. Association and risk between morbidity or mortality vs vaccination status were analysed using the Chi-square test and a simple logistic regression test.

Ethical Clearance

The study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-01816-PMS).

RESULTS

A total of 208 patients positive for COVID-19 were included in the study. The median (IQR) age for all cases was 46.5 (27.0%) with 58 (27.9%) elderly. The majority were Malay 133 (63.9%), followed by Indian 42 (20.2%), Chinese 16 (7.7%) and others 17 (8.2%). Males constituted 93 (44.7%) of the patients, and females accounted for 115 (55.3%) of the patients. About 120 (57.7%) patients had at least one underlying comorbidity, where diabetes mellitus (DM) 68 (32.7%) and hypertension (HPT) 82 (39.4%) were among the commonest illness. Most of the patients were in CAT2 79 (38%) and CAT4 76 (36.5%) while the least was in CAT1 14 (6.7%). Almost half of the patients 100 (48.1%) were categorised as severe, and about 20 (9.6%) succumbed to death during hospitalisation. Only about one-third of the patients 74 (35.6%) had two doses of vaccinations (Table I).

Further analysis showed there was no statistically significant difference between clinical COVID-19 stages with age, gender, ethnicity, and co-morbidity except for diabetes mellitus ($p < 0.012$). There were also no significant variations between the age group and disease severity ($p > 0.513$) (data not shown).

Table II showed there were statistically significantly different in FBC parameters (MPV, NLR, ANC, ALC, AMC, AEC, ABC and IG) when a comparison was done for disease severity ($p < 0.001$). It also showed a significant correlation between the FBC parameters (platelet, MPV, NLR, ANC, ALC, AEC and ABC) ($p<0.001$) with the patient's outcome (survivors vs non-survivors). (Table II).

However, we found significant changes in FBC parameters for fully vaccinated patients where it showed a significant low in NLR and MPV and a high in ALC, AMC, AEC and ABC compared to unvaccinated and partially vaccinated patients ($p < 0.001$) (Table II).

Table I : Demographic & clinical characteristics of COVID-19 patients

Variables	Category	n =208 (%)
Age, median (IQR)		46.5 (27.0)
Age group	18-59	150(72.1)
	>60	58 (27.9)
Race	Malay	133 (63.9)
	Indian	42 (20.2)
	Chinese	16 (7.7)
	Others	17 (8.2)
Gender	Male	93 (44.7)
	Female	115 (55.3)
Comorbid	No	88 (42.3)
	Yes	120 (57.7)
DM		68 (32.7)
HPT		82 (39.4)
Dyslipidaemia		25 (12.0)
CKD/ESRF		11 (5.3)
Chronic lung disease		18 (8.7)
Heart disease		15 (7.2)
Any other comorbidity		31 (14.9)
COVID-19 Stage	1	14 (6.7)
	2	79 (38.0)
	3	16 (7.7)
	4	76 (36.5)
	5	23 (11.1)
Severity	Non-severe	108 (51.9)
	Severe	100 (48.1)
Outcome	Survivor	188 (90.4)
	Death	20 (9.6)
Vaccination status	Unvaccinated	78 (37.5)
	Partially vaccinated	56 (26.9)
	Completed (2 doses)	74 (35.6)

*Abbreviations: IQR: Interquartile range, DM: Diabetes mellitus, HPT: Hypertension, CKD: Chronic kidney disease, ESRF: End-stage renal failure, SLE: Systemic Lupus Erythematosus.

A significant association was found between vaccination status and disease severity ($p< 0.001$) (Table 3.1). A regression analysis showed that unvaccinated patients were 6.85 times more likely to have severe COVID-19 disease than completely vaccinated patients ($p < 0.001$) (Table 3.2). Patients who received one dose of the COVID-19 vaccine still significantly have a high risk to develop severe COVID-19 infection, 5.20 times more to have the severe disease compared to those who completed the vaccination ($p < 0.001$) (Table 3.2).

Table 3.1 also revealed a significant association between vaccination status and patient outcome ($p < 0.001$). A logistic regression study revealed that unvaccinated patients were 18.84 times more likely to succumb to COVID-19 than patients who had already completed their vaccination (Table 3.2). Whereas patients that were partially vaccinated had no significant difference in mortality compared to those who completed vaccination (Table 3.2).

DISCUSSION

Our study showed patients with underlying DM have a significant association with COVID-19 clinical stages. It is a substantial risk factor for all kinds of infections, not only for COVID-19. The condition is associated with immune system deficiencies, particularly alterations in innate immunity (11). COVID-19 involved an interaction at multiple points including glucotoxicity in the lungs, increased thromboembolic risk, exacerbated oxidative stress and abnormally high levels of cytokine production which resulted in organ damage (11). High levels of interleukin-6 (IL-6) and reduced T-cell activity are critical in the development of COVID-19 illness in diabetics (12).

In accordance with our findings, lymphopenia has been significantly associated with COVID-19 severity and mortality and has evolved into a severe COVID-19 signature (8, 13, 14, 15). The percentage of lymphocytes dropped by 20% in severe cases (16). Further analysis of the lymphocyte subtype showed a remarkable reduction in memory T cells in severe disease, suggesting that COVID-19 patients may not establish immunity against subsequent viral infection (17). A considerable drop in T lymphocytes has been demonstrated to be strongly correlated with COVID-19 severity and mortality (16).

The mechanism of lymphopenia is multifactorial and related to lymphocyte redistribution, increased consumption, and defective haematopoiesis through a direct attack on lymphatic organs, infection of bone marrow and occurrence of cytokine storm (13,16,18). It appears to be a significant haematological abnormality that leads to the progression of an unfavourable outcome. Therefore, Mahda *et al* proposed that lymphocyte count might be a useful criterion for risk stratification of COVID-19 patients since it has been demonstrated to be significantly reduced particularly in critically ill patients (16).

Consistent with previous studies, our analysis on the monocyte, eosinophil and basophil count turns out

Table II : FBC parameters association with COVID-19 severity, patient outcome and vaccination status

FBC parameters	Med (IQR)	COVID-19 severity			Patient outcome			Vaccination status			
		Non-severe, Med (IQR)	Severe, Med (IQR)	*p*-value [a]	Survivor, Med (IQR)	Non-survivor, Med (IQR)	*p*-value [a]	Unvaccinated, Med (IQR)	Partially vaccinated, Med (IQR)	Completed vaccination, Med (IQR)	*p*-value [b]
WBC (10^9/L)	7.00 (4.50)	6.90 (4.50)	7.70 (4.60)	0.216	7.00 (4.50)	8.50 (5.30)	0.290	6.90 (4.70)	6.30 (4.50)	8.30 (3.90)	0.044 *
RBC (10^{12}/L)	4.74 (0.76)	4.67 (1.00)	4.80 (0.82)	0.136	4.73 ± 0.70)	4.73 (1.17)	0.693	4.80 (0.82)	4.87 (1.04)	4.71 (1.08)	0.416
Hb (g/L)	130.0 (26.8)	127.0 (23.8)	133.0 (24.0)	0.152	130.5 (24.8)	125.0 (57.8)	0.094	130.5 (31.8)	131.0 (25.0)	127.5 (30.0)	0.586
HCT (L/L)	0.401 (0.073)	0.401 (0.074)	0.403 (0.075)	0.447	0.402 (0.073)	0.399 (0.134)	0.549	0.401 (0.054)	0.404 (0.069)	0.407 (0.084)	0.826
MCV (fL)	85.55 (7.10)	86.20 (7.30)	85.05 (8.10)	0.081	85.85 (7.00)	83.05 (11.30)	0.051	85.05 (9.20)	84.30 (7.50)	87.10 (6.80)	0.003 *
MCH (pg)	27.85 (3.20)	27.90 (3.20)	27.80 (3.30)	0.938	27.90 (3.20)	26.90 (4.30)	0.143	27.50 (3.90)	27.70 (3.90)	28.30 (3.00)	0.053
MCHC (g/L)	325.0 (18.0)	323.0 (15.0)	327.5 (22.0)	0.015	325.0 (18.0)	323.0 (27.0)	0.559	323.5 (20.0)	327.0 (15.0)	325.0 (17.0)	0.424
Platelet (10^9/L)	215.5 (123.0)	217.0 (102.2)	213.0 (134.8)	0.235	224.0 (119.3)	141.0 (123.5)	<0.001*	205.5 (145.0)	213.5 (109.0)	231.5 (117.8)	0.078
MPV (fL)	10.3 (1.2)	10.1 (1.3)	10.6 (1.2)	<0.001 *	10.2 (1.3)	11.0 (1.1)	0.007 *	10.5 (1.1)	10.6 (1.4)	9.9 (1.1)	<0.001*
RDW-CV (%)	13.5 (1.9)	13.6 (1.8)	13.3 (2.3)	0.829	13.5 (1.8)	13.6 (3.7)	0.212	13.9 (2.5)	13.4 (1.6)	13.2 (1.5)	0.060
NLR	4.22 (5.82)	2.63 (2.20)	7.49 (6.90)	<0.001 *	3.71 (5.25)	8.24 (7.95)	<0.001*	4.81 (6.55)	5.53 (7.82)	3.31 (2.59)	0.002 *
ANC (10^9/L)	5.10 (4.03)	4.42 (3.30)	6.08 (4.34)	<0.001 *	4.96 (3.93)	7.05 (5.36)	0.025 *	5.20 (4.35)	4.70 (4.09)	5.54 (3.45)	0.687
ALC (10^9/L)	1.18 (1.11)	1.62 (1.08)	0.82 (0.62)	<0.001 *	1.29 (1.14)	0.72 (0.54)	0.002 *	1.04(1.08)	0.92 (0.77)	1.55 (1.14)	<0.001*
AMC (10^9/L)	0.44 (0.49)	0.54 (0.43)	0.21 (0.39)	<0.001 *	0.46 (0.49)	0.24 (0.45)	0.062	0.32 (0.52)	0.32 (0.45)	0.54 (0.31)	<0.001*
AEC (10_9/L)	0.01 (0.07)	0.04 (0.13)	0.00 (0.00)	<0.001 *	0.01 (0.08)	0.00 (0.00)	<0.001 *	0.00 (0.02)	0.00 (0.02)	0.06 (0.14)	<0.001*
ABC (10^9/L)	0.01 (0.01)	0.02 (0.02)	0.01 (0.02)	<0.001 *	0.01 (0.02)	0.01 (0.01)	0.020 *	0.01 (0.01)	0.01 (0.02)	0.02 (0.02)	<0.001*
IG (10^9/L)	0.03 (0.05)	0.02 (0.30)	0.03 (0.06)	<0.003 *	0.03 (0.05)	0.04 (0.06)	0.132	0.03 (0.05)	0.02 (0.03)	0.03 (0.05)	0.234

**Statistically significant at α=0.05

[a] Statistical test: Mann-Whitney U

[b] Statistical test: Kruskal-Wallis

Table 3.1 : Association between vaccination status with COVID-19 severity and patient outcome

Vaccination status	Total patient, n	COVID-19 Severity			Patient outcome		
		Survivor, n (%)	Non-survivor, n (%)	*p*-value [a]	Non-severe, n (%)	Severe, n (%)	*p*-value [a]
Unvaccinated	78	27 (34.6)	51 (65.4)	<0.001 *	62 (79.5)	16 (20.5)	<0.001*
Partially Vaccinated	56	53 (94.6)	3 (5.4)		53 (94.6)	3 (5.4)	
Completed vaccination	74	73 (98.6)	1 (1.4)		73 (98.6)	1 (1.4)	

** Statistically significant at α=0.05

[a] Statistical test: Chi-square

Table 3.2 : Predictability of COVID-19 severity and their outcome based on the vaccination status

Vaccination status	COVID-19 severity		Patient outcome	
	Odds Ratio (95% CI)	*p*-value [a]	Odds Ratio (95% CI)	p-value [a]
Unvaccinated	6.85	<0.001*	18.84	0.005*
Partially vaccinated	5.20	<0.001*	4.13	0.225
Completed vaccination	1	Ref.	1	Ref.

** Statistically significant at α=0.05

[a] Statistical test: Simple logistic regression

to be much lower in severe and non-survivor patients (9, 21). However, a few studies found no significant differences in monocytes when comparing severe and non-severe groups (2, 13).

The changes in AMC, AEC and ABC in COVID-19 were still unclear and many researchers thought it involved a multifactorial interrelationship. Cytokine synthesis, phagocytic activity, lymphocyte engagement, macrophages and monocytes play crucial roles in the innate and adaptive immune responses in the battle against microbial and viral diseases (19). During acute infection, the hyperinflammatory reaction may dampen the activity and count of monocyte, eosinophil and basophils leading to their reduction (20). It also could be related to acute respiratory distress syndrome leading to their recruitment into the pulmonary organ. Eosinopenia is possibly due to their movement to other tissues, which is also observed with various viral infections (21).

Our study showed significantly increased NLR, ANC, and reduced ALC in severe and poor outcome patients which were consistent with many reports (8, 9, 23). Much research has been conducted to evaluate the relationship between NLR and prognosis in COVID-19 patients. An elevated neutrophil count along with a low lymphocyte count is an indicator of an increased NLR. It is the main indicator of systemic inflammation and is commonly used to predict patient outcomes in bacterial infections. In severe cases of COVID-19, the white blood cells shift toward neutrophils rather than lymphocytes, indicating that NLR might aid in risk-stratifying patients (22). Patients with NLR values of more than 6.5 had a poor prognosis and those with NLR values of more than 9 were more likely to die (24). It implies that this marker is a rapid, simple and highly effective screening tool for patients who need to be evaluated precisely due to their high vulnerability (25).

Conversely, our result showed in fully vaccinated patients, NLR was low but high in ALC, AMC, AEC and ABC. Low NLR, especially after a booster dose suggestive of a successful immune response (26, 27). Lymphocytes (T cells) defend both naturally infected and vaccinated individuals (26). It has been identified to detect and defend against the delta variant of SARS-CoV-2, the virus that causes COVID-19 (26). Innate immunity includes monocytes, eosinophils and basophils which account for only 0.01% of all circulating blood cells before vaccination had shown significantly high following vaccination. After the second vaccination, monocyte and basophils expanded 100-fold to account for 1% of all blood cells indicating that their disposition changed from an inflammatory to an antiviral (28). AEC, AMC and ABC have antiviral activity and may be an indicator of COVID-19 improvement (29).

Our platelets count analysis revealed that individuals who died from COVID-19 had considerably lower platelets count than those who survived which was consistent with the majority of previous studies. Yang et al. also found that 20% of COVID-19 patients in their study had thrombocytopenia which correlated

with worse patient outcomes (23). However, Liu *et al.* reported no significant difference in platelet count with mortality (30). There have been several proposed mechanisms for the thrombocytopenia brought on by COVID-19 which include direct viral infection, megakaryocyte and bone marrow suppression, destruction of bone marrow progenitors, decreased thrombopoietin and inflammatory cytokines.

Whereas our analysis of MPV showed significantly higher in severe and poor outcome patients which supports previous studies (31,32,33). High MPV indicates the presence of increased immature platelets that are functionally, metabolically, and enzymatically active and can cause significant prothrombotic potential. The variation of both MPV and platelet count was consistent with acute inflammation conditions.

Our results showed that IG was higher in severe COVID-19 patients than in non-severe, which supported previous studies (8, 35). Inflammation in many infectious disorders has been associated with the premature release of IG from the bone marrow into peripheral circulation (34). The increase in number and the reduction of mature neutrophils are more likely due to the progressive and continuous mobilisation of these cells in response to ongoing inflammation, resulting in the premature release of IG from the bone marrow (34). High levels of circulating IGs are associated with advanced stages of COVID-19 as well as thromboembolic consequences (36). IG count has the potential to serve as a reliable biomarker, which would be of great use in predicting the severity and consequences of COVID-19 infection (34). NLR value combined with IG rather than neutrophil count alone was suggested as a better severity predictor of COVID-19 (8).

Vaccination is thought to be the most efficient method of limiting the pandemic. Initially, vaccination safety was a big issue for the public leading to vaccine hesitation. It has been shown vaccination successfully prevents disease progression and reduces hospitalisation, severity and mortality rates worldwide (37). Our study also showed vaccination had a significant association with disease severity and mortality. Both the unvaccinated and partially vaccinated patients were likely to have severe diseases compared to patients who had completed 2 doses of vaccination. Completely vaccinated patients were less likely to have severe COVID-19 disease. The second dosage of a COVID-19 vaccine stimulates the immune system that provides broad antiviral protection. This brings up the importance of completing two doses of vaccine. Even though humoral immune response dropped off six months after vaccination, cellular immunity remains strong suggesting that T cells defend both natural infection and vaccinated individuals (26).

However, our result showed mortality has no significant association between partially or completely vaccinated patients, implying that receiving only one dose of vaccine does help in reducing the severity of the disease only. Whereas unvaccinated patients were 18 times higher to succumb to COVID-19 than those who had received two doses of COVID-19 vaccination.

CONCLUSION

Deep knowledge of FBC variations in COVID-19 in our population could lead to accurate clinical predictions of disease conditions. Upon admission, ANC, NLR, MPV and IG are significantly higher, while ALC, AEC, AMC and ABC are significantly lower in the severe COVID-19 patients and the non-survivors compared to the non-severe patients and the survivors. After 2 doses of vaccination, the changes in FBC parameters suggest that COVID-19 vaccines are extremely successful in preventing severe illness and death.

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