Haematological profile of COVID-19 patients from a centre in Singapore

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ABSTRACT

Background: Haematological markers such as absolute lymphopenia have been associated with severe COVID-19 infection. However, in the literature to date, the cohorts described have typically included patients who were moderate to severely unwell with pneumonia and who required intensive care. It is uncertain if these markers apply to a population with less severe illness. We sought to describe the haematological profile of patients with mild disease with COVID-19 admitted to a single centre in Singapore.

Methods: We examined 554 consecutive PCR positive SARS-COV-2 patients admitted to a single tertiary healthcare institution from Feb 2020 to April 2020. In all patients a full blood count was obtained within 24 h of presentation.

Results: Patients with pneumonia had higher neutrophil percentages (66.5 ± 11.6 vs 55.2 ± 12.6%, p < 0.001), lower absolute lymphocyte count (1.5 ± 1.1 vs 1.9 ± 2.1 x109/L, p < 0.011) and absolute eosinophil count (0.2 ± 0.9 vs 0.7 ± 1.8 x109/L, p = 0.002). Platelet counts (210 ± 56 vs 230 ± 61, p = 0.020) were slightly lower in the group with pneumonia. We did not demonstrate significant differences in the neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in patients with or without pneumonia. Sixty-eight patients (12.3%) had peripheral eosinophilia. This was more common in migrant workers living in dormitories.

Conclusion: Neutrophilia and lymphopenia were found to be markers associated with severe COVID-19 illness. We did not find that combined haematological parameters: neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio had any association with disease severity in our cohort of patients with mild-moderate disease. Migrant workers living in dormitories had eosinophilia which may reflect concurrent chronic parasitic infection.

Introduction

Haematological abnormalities have been described in COVID-19 patients [1]. These patients demonstrate various degrees of leukopenia and lymphopenia. Haematological variations have also been shown to correlate with disease severity and prognosis. The existing literature suggests that neutrophilia and lymphopenia are typically seen in severe cases, and both are early prognosticators of severity. T cell counts (CD4, CD8) were also seen to be decreased in patients with severe disease [2]. The mechanisms behind lymphopenia are not presently fully elucidated, but Tavakolpour et al have postulated that the inflammatory cytokine storm (including elevated interleukin-6 levels) may be closely associated with lymphopenia [3].

Combined haematological parameters including neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR) of COVID-19 patients have been shown to be increased compared to healthy controls in several studies [4,5]. In a study of 116 Chinese patients of which 23% were considered patients with severe disease NLR had a greater prognostic value for severe disease than the other two combination parameters MLR and PLR [6].

There is a paucity of data on the role eosinophils have, if any, in COVID-19. It has been postulated that eosinophils can exert potent proinflammatory effect, and are also implicated in immunoregulation and anti-viral activity. In a study of 140 community-acquired COVID-19 infected patients, of which 58 of 140 (41%)
were regarded as severe, from Wuhan, China, eosinopenia (defined as < 100 cells/mm³) was associated with more severe COVID-19 infection, and acute respiratory deterioration [7].

In this study, we sought to profile patients with less severe COVID-19 illnesses and examine associations between their disease severity, sequelae and haematological characteristics.

**Methods**

In Singapore, all patients with COVID-19 were initially hospitalized as tertiary hospitals had been used as quarantine facilities at the start of the pandemic, prior to the construction of purpose-built community isolation facilities.

We examined the electronic medical records of 554 consecutive patients admitted to our institution from 23rd January 2020 to 30th April 2020 who were confirmed to have COVID-19 based on a positive polymerase chain reaction (PCR) test from a nasopharyngeal swab [8]. There were no patients excluded or lost to follow-up. Data collected for each patient included their demographic backgrounds, past medical history, and their presenting symptoms. The presenting day of illness was derived based on the number of days from symptom onset to the day of hospital admission.

All patients had a baseline haematological profile performed (full blood count examination, FBC) obtained within 24 h of admission, and chest X-ray performed. We followed patients for clinical outcomes during the hospital admission, including data on patients who required intensive care, mechanical ventilation and adverse clinical outcomes such as myocarditis/myocardial injury [9–11] and death. Persistent fever was defined as a fever (37.5 degree Celsius and above) lasting over a 72-hour period. Pneumonia was defined by the presence of radiographic evidence of infiltrates on plain chest radiograph or computed tomography (if performed).

We divided the study population based on the presence of pneumonia, and compared their baseline clinical and haematological profiles. We also compared patients based on the presence of peripheral eosinophilia (>0.5 × 10⁹/L) on their initial FBC [12]. The severity of COVID-19 illness was defined based on the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) where mild cases were defined as cases where symptoms were mild and there was no evidence of pneumonia on chest radiography. Moderate cases were defined as cases with fever, respiratory symptoms and had radiological evidence of pneumonia. Severe cases were defined as cases with at least one of the three features of: tachypnoea with respiratory rate greater than 30, mean oxygen saturation less than 93%, fractional inspired oxygen less than 300mmHg [13].

Imported cases were those who acquired COVID-19 overseas and returned to Singapore. Locally transmitted cases were defined as those who acquired COVID-19 within the community in Singapore and have not travelled overseas. Dormitory cases were defined as those who acquired COVID-19 as a consequence of living or working in foreign worker dormitories. All treatment with anti-viral drugs were done in consultation with infectious disease physicians and/or as part of research trial protocols. Empiric treatment of eosinophilia with albendazole and ivermectin were done after consultation with an infectious disease physician.

To compare these groups, Student’s t-tests were used for continuous parameters and the data was presented in the form of means (±standard deviation). Categorical parameters were compared by Chi-squared tests, and the data was presented in frequencies and percentages. A p-value of less than 0.05 was considered significant. All data analysis was done on SPSS version 20.0 (SPSS, Inc., Chicago, Illinois). This study was approved by the hospital’s institutional review board (National Healthcare Group (NHG) Domain Specific Review Board (DSRB) 2020/00545) prior to the conduct of the study. Data collected was anonymised and a waiver of informed consent had been obtained from the institutional review board.

**Results**

**Demographics and clinical presentation**

Of the 554 patients studied, 57 (10.3%) had radiological evidence of pneumonia. These patients tended to be older (49 ± 13 vs 36 ± 11 years, p < 0.001) and were more likely to have other medical comorbidities such as hypertension (32.6% vs 9.8%, p < 0.001), hyperlipidaemia (33.3% vs 5.0%, p < 0.001), and diabetes mellitus (16.3 vs 1.1%, p < 0.001). Patients with pneumonia were more likely to require oxygen supplementation (14.0% vs 1.6%, p < 0.001), require intensive care (23.2% vs 1.2%, p < 0.001) and mechanical ventilation (19.3% vs 1.0%, p < 0.001) and receive treatment with lopinavir/ritonavir (26.3 vs 4.4%, p < 0.001) and remdesivir (17.5% vs 1.6%, p < 0.001). There were 2 deaths (0.5%) out of 554 patients, and both patients had pneumonia (Table 1).

**Haematological profiles of patients with pneumonia**

There was no significant difference in the total white cell count in patients with or without pneumonia. The absolute lymphocyte count (1.5 ± 1.1 vs 1.9 ± 2.1 × 10⁹/L, p < 0.011), eosinophil count (0.2 ± 0.9 vs 0.7
± 1.8 × 10^9/L, \( p = 0.002 \)), monocyte count (0.6 ± 0.3 vs 0.9 ± 1.4 × 10^9/L, \( p < 0.001 \)) and platelet count was lower in COVID-19 patients with pneumonia (Table 1).

We did not find any significant differences in the neutrophil-lymphocyte ratio (NLR) (4.3 ± 4.3 vs 3.0 ± 7.2, \( p = 0.194 \)), monocyte-lymphocyte (MLR) ratio (2.9 ± 1.9 vs 3.1 ± 4.3, \( p = 0.690 \)) or platelet-lymphocyte ratio (PLR) (186.4 ± 95.9 vs 161.2 ± 334.5, \( p = 0.576 \)) between patients with or without pneumonia (Table 1).

### Patients with and without eosinophilia

A total of 68 patients (12.3%) had eosinophilia based on their initial FBC.

When compared to patients without eosinophilia, fewer patients with eosinophilia had pneumonia (1 (1.5%) vs 56 (11.5%); \( p = 0.005 \)). Patients with eosinophilia were younger (33.2 ± 9.4 vs 37.4 ± 11.9 years, \( p = 0.006 \)), and were largely Indian and Bangladeshi migrant workers living in dorms (\( n = 62, 91.2\% \)). Three patients with eosinophilia acquired COVID-19 through local transmission (\( n = 3, 4.4\% \)) and 3 via overseas exposure.

Patients with eosinophilia did not differ based on their medical comorbidities each as hypertension, hyperlipidaemia or diabetes mellitus. None of the patients with eosinophilia reported having atopic conditions such as asthma and atopic dermatitis. The severity of COVID-19 illness did not differ between the group with eosinophilia and the group without (Table 2).

### Discussion

The main findings of this study are that patients with pneumonia were more likely to have neutrophilia and lymphopenia. We also found a substantial

| Parameter | Overall (n = 554) | Pneumonia (n = 57) | No Pneumonia (n = 497) | \( p \)-value |
|-----------|------------------|-------------------|-----------------------|----------------|
| Age (years) | 37 (±12) | 49 (±13) | 36 (±11) | <0.001 |
| Gender (Male) | 477 (86.9%) | 41 (71.9%) | 437 (88.6%) | <0.001 |
| Past Medical History | | | |
| Hypertension | 53 (12.3%) | 15 (32.6%) | 38 (8.9%) | <0.001 |
| Hyperlipidaemia | 34 (8.1%) | 15 (33.3%) | 19 (5.0%) | <0.001 |
| Diabetes mellitus | 21 (5.1%) | 7 (16.3%) | 14 (3.8%) | <0.001 |
| Asthma | 6 (1.5%) | 4 (1.1%) | 4 (1.1%) | 0.055 |
| No previous medical conditions | 367 (90.4%) | 24 (60.0%) | 343 (92.7%) | <0.001 |

**Clinical profile**

| Asymptomatic illness | 66 (11.9%) | 4 (7.0%) | 62 (12.5%) | 0.228 |
| Length of days with fever | 1.2 (±2.4) | 3.1 (±3.1) | 1.0 (±2.2) | <0.001 |
| Oxygen saturation (%) | 98 (±3) | 96 (±7) | 98 (±1) | <0.001 |

**Laboratory Investigations**

| Parameter | Overall (n = 554) | Pneumonia (n = 57) | No Pneumonia (n = 497) | \( p \)-value |
|-----------|------------------|-------------------|-----------------------|----------------|
| Total White Cell Count | 6.5 (±2.2) | 6.5 (±2.9) | 6.5 (±2.1) | 0.975 |
| Absolute neutrophil count | 4.2 (±7.9) | 4.5 (±2.7) | 4.2 (±8.3) | 0.545 |
| Neutrophil percentage | 56.3 (±12.9) | 66.5 (±11.6) | 55.2 (±12.6) | <0.001 |
| Absolute lymphocyte count | 1.9 (±2.0) | 1.5 (±1.1) | 1.9 (±2.1) | 0.011 |
| Lymphocyte percentage | 28.2 (±11.1) | 22.7 (±10.1) | 28.9 (±11.1) | <0.001 |
| Absolute eosinophil count | 0.61 (±1.7) | 0.2 (±0.9) | 0.7 (±1.8) | 0.002 |
| Eosinophil percentage | 2.4 (±3.3) | 1.0 (±1.4) | 2.5 (±3.4) | 0.001 |
| Absolute monocyte count | 0.9 (±1.3) | 0.6 (±0.3) | 0.9 (±1.4) | <0.001 |
| Monocyte percentage | 11.9 (±5.6) | 9.4 (±3.8) | 12.2 (±5.7) | <0.001 |
| Absolute basophil count | 0.04 (±0.09) | 0.02 (±0.02) | 0.04 (±0.09) | 0.082 |
| Basophil percentage | 0.6 (±1.3) | 0.3 (±0.2) | 0.6 (±1.3) | <0.001 |
| Haemoglobin (g/dL) | 14.9 (±1.6) | 14.1 (±1.8) | 15.0 (±1.6) | 0.002 |
| MCV (fL) | 84.9 (±58) | 86.0 (±47) | 84.7 (±59) | 0.108 |
| Haematocrit | 45.5 (±23.3) | 41.7 (±5.3) | 46.0 (±24.7) | 0.202 |
| Platelets | 228 (±61) | 210 (±56) | 230 (±61) | 0.020 |
| Neutrophil/Lymphocyte Ratio | 3.2 (±7.0) | 4.3 (±4.3) | 3.0 (±7.2) | 0.194 |
| Monocyte/Lymphocyte Ratio | 3.1 (±4.1) | 2.9 (±1.9) | 3.1 (±4.3) | 0.690 |
| Platelet/Lymphocyte Ratio | 163.8 (±118.4) | 186.4 (±95.9) | 161.2 (±334.5) | 0.576 |
| Eosinophil/Lymphocyte Ratio | 0.37 (±1.12) | 0.16 (±0.80) | 0.39 (±1.15) | 0.138 |
| Creatinine (mmol/L) | 79 (±30) | 88 (±78) | 78 (±18) | 0.019 |
| LDH | 436 (±423) | 644 (±77) | 414 (±360) | <0.001 |
| C-reactive protein | 14 (±27) | 40 (±43) | 11 (±23) | <0.001 |
| Ferritin | 179 (±216) | 353 (±385) | 164 (±187) | <0.001 |
| Treatment | | | |
| Lopinavir/Ritonavir | 37 (6.6%) | 15 (26.3%) | 22 (4.4%) | <0.001 |
| Remdesivir | 18 (3.2%) | 10 (17.5%) | 8 (1.6%) | <0.001 |
| Hydroxychloroquine | 3 (0.5%) | 5 (3.5%) | 0 (0.0%) | <0.001 |
| Length of hospital stay (days) | 10.2 (±13.3) | 10.6 (±7.7) | 15.1 (±18.2) | <0.001 |
| Requiring oxygen | 16 (2.9%) | 8 (14.0%) | 8 (1.6%) | <0.001 |
| Persistent fever >72h | 40 (7.3%) | 16 (29.1%) | 24 (4.8%) | <0.001 |
| Required intensive care monitoring | 19 (3.4%) | 13 (23.2%) | 6 (1.2%) | <0.001 |
| Required mechanical ventilation | 16 (2.9%) | 11 (19.3%) | 5 (1.0%) | <0.001 |
| Myocarditis/myocardial injury | 3 (0.7%) | 3 (7.3%) | 0 (0.0%) | <0.001 |
| Death | 2 (0.5%) | 2 (3.5%) | 0 (0.0%) | <0.001 |
Table 2. Characteristics of patients with Eosinophilia.

| Parameter                        | Eosinophilia (n = 68) | No Eosinophilia (n = 486) | p-value |
|----------------------------------|-----------------------|---------------------------|---------|
| Age (years)                      | 33.2 (±9.4)           | 37.4 (±11.9)              | 0.006   |
| Male gender                      | 62 (91.2%)            | 416 (86.3%)               | 0.265   |
| Ethnicity                        |                       |                           |         |
| Chinese                          | 6 (8.8%)              | 85 (17.5%)                |         |
| Malay                            | 2 (2.9%)              | 32 (6.6%)                 |         |
| Indian                           | 36 (52.9%)            | 163 (33.5%)               |         |
| Bangladeshi                      | 20 (29.4%)            | 155 (31.9%)               |         |
| Others                           | 4 (5.9%)              | 51 (10.4%)                |         |
| Exposure history                 |                       |                           | 0.006   |
| Overseas exposure                | 3 (4.4%)              | 26 (5.3%)                 |         |
| Local transmission               | 3 (4.4%)              | 97 (20.0%)                |         |
| Dormitory cases                  | 62 (91.2%)            | 363 (74.7%)               |         |
| Laboratory findings              |                       |                           |         |
| Lymphocyte count (×10⁹/L)        | 1.99 (±0.70)          | 1.89 (±2.14)              | 0.696   |
| Eosinophil count (×10⁹/L)        | 4.06 (±3.09)          | 0.12 (±0.12)              | <0.001  |
| Eosinophil/Lymphocyte Ratio      | 2.48 (±2.25)          | 0.07 (±0.08)              | <0.001  |
| Outcomes                         |                       |                           |         |
| Pneumonia                        | 1 (1.5%)              | 56 (11.5%)                | 0.005   |
| Acute kidney injury              | 2 (2.9%)              | 43 (8.8%)                 | 0.150   |
| Required mechanical ventilation  | 0 (0.0%)              | 16 (3.3%)                 | 0.240   |

The study finding that more unwell patients had neutrophilia and lymphopenia corroborates with the findings of another meta-analysis of 4,969 patients from 22 studies studying haematological parameters in COVID-19 patients (ref). In this meta-analysis, lymphopenia conferred more than a 3-fold increase in the odds of both severe and fatal COVID-19, and neutrophilia was associated with a more than 7-fold increase in the odds for severe disease and fatal disease [14]. Although the mechanisms for neutrophilia and lymphopenia are not completely elucidated, lymphopenia is thought to arise from direct cytopathic effects and increased apoptosis from deranged cytokine milieu, and results in maladaptive antiviral response, rendering the human host susceptible to severe hyperinflammatory immunopathology [15]. In mouse models of severe acute respiratory syndrome (SARS), CD4+ lymphopenia was shown to cause increased immune mediated pneumonitis [16]. Neutrophilia, as well as neutrophil infiltration in pulmonary capillaries, acute capillaritis with fibrin deposition, neutrophilic mucositis and extravasation of neutrophils into alveolar spaces, have been observed in autopsy studies of COVID-19 patients.

One of the forces of neutrophilic driven lung injury is postulated to be related to neutrophil extracellular traps (NETs) [17]. NETs are extracellular webs of chromatin, proteins, and oxidant enzymes which neutrophils release in order to contain infection. However, when dysregulated, NETs have the potential to propagate inflammation and microvascular thrombosis in the lungs of COVID-19 patients. Recent studies analysing the serum of COVID-19 patients found that COVID-19 sera could trigger otherwise healthy neutrophils to release NETs [18,19].

Other markers of severity have emerged in literature [20,21]; notably the neutrophil/lymphocyte ratio had garnered interest where a high NLR was associated with more severe disease. In this study, we were unable to demonstrate significant differences in the NLR between those with pneumonia and those without.

Abnormalities in eosinophil count in our cohort may be better attributed to chronic parasitic infections

Out of 554 patients, 68 (12.3%) patients in this study exhibited peripheral eosinophilia. These patients were younger (33.2 ± 9.4 vs 37.4 ± 11.9 years, p = 0.006), and were predominantly Indian or Bangladeshi foreign migrant workers residing in dormitories. These patients did not otherwise have or report atopic conditions which might otherwise have accounted for the rise in eosinophils. On account of cost limitations, they were not otherwise evaluated for the underlying cause of eosinophilia. Most patients came from countries where parasitic infections are endemic, and thus an assumption was made that the eosinophilia seen was likely due to asymptomatic chronic parasitic infection. Since eosinophilia was largely seen in a group of migrant dorm workers with mild disease, and was not seen in non-migrant-dorm-workers who also had mild infection, it is unlikely that there is any association between the eosinophilia and COVID-19 infection. Eleven patients were empirically treated with albendazole or Ivermectin on the assumption of chronic parasitic infection.

Overall, the evidence on the role of eosinopenia reflecting more severe disease is mixed. Henry et al., who had pooled data of four different studies of 347 patients [22], found very modest difference of eosinophil count in COVID-19 patients with severe illness compared to those with milder disease [weighted mean difference (WMD), −0.01 × 10⁹/l; 95% confidence interval (95% CI), −0.02 to −0.01 × 10⁹/l]. There was notably high heterogeneity (I², 74.4%) amongst the pooled studies. Ghahramani et al. in a meta-analysis [23], examined the results of five different studies and found modest and only a marginally significant difference of eosinophil count in COVID-19 patients with severe illness compared to those with milder disease (WMD, −0.03 × 10⁹/l; 95% CI, −0.05 to −0.00 × 10⁹/l), reporting again very high heterogeneity (I², 86%).

In a meta-analysis of 1228 patients from 10 studies, Huang et al [24] showed that when compared to patients with non-severe COVID-19 infections (patients who had either mild pneumonia, moderate pneumonia, non-critical disease or recovery group), patients in the severe group (severe pneumonia, critical
pneumonia, critical disease and death group) had strikingly lower average eosinophil counts (standard mean difference 0.65, 95% confidence intervals [CI] 0.29–1.01; P < .001).

Previous studies describe that increased inflammation leads to lower counts of eosinophils, and an increased eosinophil count could be associated with a better prognosis for COVID-19, including the lower incidence of complications and mortality. Molecular mechanisms thought to explain this phenomenon include the discovery of CD101—eosinophils increasing more rapidly and briefly than the neutrophils, secreting Protectin-D1 through Alox15-mediation to reduce the accumulation of inflammatory cells and reduce inflammatory factors [25].

In our study, the finding that fewer patients with eosinophilia developed pneumonia may be accounted for by the fact that eosinophilia occurred in migrant dorm workers who were a young with fewer co-morbidities and were thus at less risk of severe disease [8].

**Strengths and limitations**

Each patient’s clinical progress was only evaluated within the hospital admission and we were not able to longitudinally examine patients for longer-term sequelae of the disease. We were not able to review the effects after antiparasitic treatment to determine whether this empiric treatment improved eosinophilia. This particular cohort of patients with largely mild disease (only 11/554 patients (1.8%) had severe disease) might not have sufficient power to validate other haematological biomarkers of severity found to have clinical utility in other studies.

**Conclusions**

Consistent with other studies, neutrophilia and lymphopenia appear to be sufficiently sensitive markers of severe COVID-19 illness even in a cohort of patients where only 1.8% had severe COVID-19 disease. We did not find that combined haematological parameters; NLR, MLR and PLR, had any association with disease severity in our cohort of patients with largely mild to moderate disease. We found that a substantial proportion of migrant worker living in dormitories had eosinophilia which was assumed to reflect the probability of concurrent chronic parasitic infection.

**Disclosure statement**

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