Differences in Prevalence of Haematological Abnormalities on Presentation to Hospital in COVID-19-Infected Adult and Paediatric Patients: A Retrospective Multicentre Descriptive Study

Saubia Fathima\textsuperscript{a} Salma Rahma\textsuperscript{b} Farah Chughtai\textsuperscript{b} Laila Al Dabal\textsuperscript{b}

\textsuperscript{a}Internal Medicine, Rashid Hospital, Dubai Health Authority, Dubai, UAE; \textsuperscript{b}Infectious Disease Department, Rashid Hospital, Dubai Health Authority, Dubai, UAE

\textbf{Keywords}\nCOVID-19 infection · Haematological manifestations · United Arab Emirates · Lymphopenia · Inflammatory markers

\textbf{Abstract}\n\textbf{Background:} It is well known that COVID-19 infection affects multiple systems in the body. Reports have documented many changes in the hematopoietic system in the pathophysiology of the disease, and many haematological markers like lymphopenia and high d dimer have been linked to worse outcomes after COVID-19 infection in adult patients. 
\textbf{Aim:} The aim of the study was to find out the prevalence and any significant difference in routine haematological parameters on presentation in paediatric and adult patients with COVID-19 infection. 
\textbf{Methodology:} We conducted a multicentre retrospective descriptive observational study and investigated the prevalence of haematological abnormalities at the presentation of 1,000 PCR swab-confirmed COVID-19-infected randomly selected adult and paediatric patients admitted to 3 tertiary hospitals in Dubai from 15 March–30 May 2020. Data were gathered through their electronic medical records, and all analysis was done using the Statistical Package for the Social Sciences software (SPSS). 
\textbf{Results:} The prevalence of at least one abnormal haematological parameter was 95.1% (794/835) on the first presentation to the hospital. After adjusting of age and gender, the prevalence of any white cell abnormality was 34.7% (290/835) (5.7% leucopenia, 9.6% leucocytosis, 25.4% lymphopenia, 5.5% neutropenia, 16.4% neutrophilia, 7.3% monocytosis, and 1.2% eosinopenia). A prevalence of 15.3% (128/835) anaemia, 9.5% (79/835) thrombocytopenia, and 4.3% (36/835) thrombocytosis was also observed. The prevalence of other abnormal blood parameters was C-reactive protein 69.5% (573/835), D dimer 57.5% (280/835), high lactate dehydrogenase 52% (383/835), high ferritin 72.1% (452/835), high international normalized ratio 5.1% (38/835), prolonged prothrombin time 32.2% (240/835), and prolonged activated partial thromboplastin time 35.6% (264/835). A significant difference in the prevalence of these abnormalities was evident between adult and paediatric populations, and these abnormalities were much more prevalent in adults but interestingly paediatric population tended to have a higher incidence of neutropenia, eosinophilia, and monocytosis (p < 0.001). 
\textbf{Conclusion:} COVID-19 infection tends to be milder and has better outcomes in the paediatric population. The immune system responds differently to the infection in these populations. The response is exaggerated in adults reflected by the increased prevalence of haematological abnormalities like raised inflammatory markers and other white cell abnormalities and has been linked with increased severity of infection and mortality.

© 2022 The Author(s).
Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission.

Correspondence to: Saubia Fathima, saubiafathima@gmail.com
Table 1. Patient characteristics and outcome of admission

|                          | Adults (N=731) | Paediatrics (N=104) |
|--------------------------|---------------|---------------------|
| n (%)                    | 731 (87.5)    | 104 (12.4)          |
| Age, years, mean ± SD    |               |                     |
| Male, N (%)              | 447.2 ± 12.8  | 49 ± 4.3            |
| Female, N (%)            | 639 (87.4)    | 55 (2.8)            |
| Comorbidities, N (%)     |               |                     |
| Diabetes mellitus        | 200 (27.3)    | 0 (0)               |
| Hypertension             | 157 (21.5)    | 0 (0)               |
| Ischemic heart disease   | 26 (3.5)      | 0 (0)               |
| CKD                      | 9 (1.2)       | 0 (0)               |
| Final outcomes, N (%)    |               |                     |
| Death                    | 93 (12.7)     | 0 (0)               |
| Discharged               | 576 (78.7)    | 102 (98.1)          |
| Transferred to another facility | 62 (8.5) | 2 (1.9)            |
| Variable                  | Total patients | Adults | Paediatrics | Asymptotic significance (2-sided) (χ² test) |
|--------------------------|----------------|--------|-------------|-------------------------------------------|
| White blood cells, n (%) |                |        |             |                                           |
| Within normal limits for age | 707 (84.7)   | 610 (83.4) | 97 (93.3)  | 0.002                                     |
| Low for age               | 48 (5.7)      | 41 (5.6) | 7 (6.7)     |                                           |
| High for age              | 80 (9.6)      | 80 (10.9) | 0 (0)       |                                           |
| Haemoglobin, n (%)        |                |        |             |                                           |
| Within normal limits for age | 707 (84.7)   | 617 (84.4) | 90 (86.5)  | NS                                        |
| Low for age               | 128 (15.3)    | 114 (15.6) | 14 (13.5)  |                                           |
| High for age              | 0 (0)         | 0 (0)   | 0 (0)       |                                           |
| Platelets, n (%)          |                |        |             |                                           |
| Within normal limits for age | 720 (86.2)   | 623 (85.2) | 97 (93.3)  | NS                                        |
| Low for age               | 79 (9.5)      | 75 (10.3) | 4 (3.3%)    |                                           |
| High for age              | 36 (4.3)      | 33 (4.5) | 3 (2.90)    |                                           |
| Lymphocytes, n (%)        |                |        |             |                                           |
| Within normal limits for age | 616 (73.8)   | 516 (70.6) | 100 (96.2) | Less than 0.001                            |
| Low for age               | 212 (25.4)    | 208 (28.5) | 4 (3.8)    |                                           |
| High for age              | 7 (0.8)       | 7 (1.0)  | 0 (0)       |                                           |
| Neutrophils, n (%)        |                |        |             |                                           |
| Within normal limits for age | 770 (92.2)   | 680 (93.0) | 90 (86.5)  | 0.02                                      |
| Low for age               | 4 (0.5)       | 4 (0.5)  | 0 (0.0)     |                                           |
| High for age              | 61 (7.3)      | 47 (6.4) | 14 (13.5)   |                                           |
| Monocytes, n (%)          |                |        |             |                                           |
| Within normal limits for age | 831 (99.5)   | 729 (99.7) | 102 (98.1) | NS                                        |
| Low for age               | 0 (0)         | 0 (0)   | 0 (0)       |                                           |
| High for age              | 4 (0.5)       | 2 (0.3)  | 2 (1.9)     |                                           |
| Basophils, n (%)          |                |        |             |                                           |
| Within normal limits for age | 818 (98.0)   | 728 (99.6) | 90 (86.5)  | Less than 0.001                           |
| Low for age               | 10 (1.2)      | 0 (0)   | 10 (9.6)    |                                           |
| High for age              | 7 (0.8)       | 3 (0.4)  | 4 (3.8)     |                                           |
| Eosinophils, n (%)        |                |        |             |                                           |
| Within normal limits for age | 207 (42.5)   | 169 (39.3) | 38 (66.7)  | Less than 0.001                           |
| Low for age               | 280 (57.5)    | 261 (60.7) | 19 (33.3)  |                                           |
| High for age              | 385 (52.0)    | 374 (58.6) | 9 (9.2)     | Less than 0.001                           |
| CRP, n (%)                |                |        |             |                                           |
| Within normal limits      | 251 (30.5)    | 115 (21.5) | 96 (92.3)  | Less than 0.001                           |
| High                      | 573 (69.5)    | 565 (78.5) | 8 (7.7)    |                                           |
| D dimer, n (%)            |                |        |             |                                           |
| Within normal limits      | 207 (42.5)    | 169 (39.3) | 38 (66.7)  | Less than 0.001                           |
| High                      | 280 (57.5)    | 261 (60.7) | 19 (33.3)  |                                           |
| LDH, n (%)                |                |        |             |                                           |
| Within normal limits for age | 353 (48.0)   | 264 (41.4) | 89 (90.8)  | Less than 0.001                           |
| High for age              | 383 (52.0)    | 374 (58.6) | 9 (9.2)     |                                           |
| INR, n (%)                |                |        |             |                                           |
| Within normal limits for age | 708 (94.9)   | 612 (94.4) | 96 (98)    | NS                                        |
| High for age              | 38 (5.1)      | 36 (5.6) | 2 (2)       |                                           |
| PT, n (%)                 |                |        |             |                                           |
| Within normal limits      | 506 (67.8)    | 433 (66.8) | 73 (74.5)  | NS                                        |
| Prolonged                 | 240 (32.2)    | 215 (33.2) | 25 (25.5)  |                                           |
| aPTT, n (%)               |                |        |             |                                           |
| Within normal limits      | 470 (63.4)    | 414 (64.4) | 56 (57.1)  | NS                                        |
| Prolonged                 | 264 (35.6)    | 6 (0.9)  | 1 (1.0)     |                                           |
| Ferritin, n (%)           |                |        |             |                                           |
| Within normal limits for age | 166 (26.5)   | 110 (19.5) | 56 (87.5)  | Less than 0.001                           |
| Low for age               | 9 (1.4)       | 4 (0.7)  | 5 (7.8)     |                                           |
| High for age              | 452 (72.1)    | 449 (79.8) | 3 (4.7)    |                                           |

CRP, C-reactive protein; LDH, lactate dehydrogenase; INR, international normalized ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time.
Research Ethics
The identity of the patient was kept confidential at all times. Since it was an observational study, there was effect of the study on the treatment of the patient.

Patient Population
A total of 835 patients were studied. 731 were studied in the adult group, and 104 patients were studied in the paediatric group. Patient characteristics and final outcomes are reported in Table 1.

Results
The mean ages were 44.7 ± 12.8 years and 4.9 ± 4.3 years in adult and paediatric groups, respectively, as described in Table 1. In the paediatric group, most patients 49% (50/104) were above the age of 3 years, while infants (below the age of 1 year) formed 22.1% (23/104) and toddlers (age 1–3 years) formed 28.8% (30/104) of the population.

There were no mortalities in the paediatric population, while 12.7% (93/731) of COVID-19 infections in adults resulted in death and 8.4% (62/731) of adult patients were transferred to another facility so their outcome is not known. The prevalence of at least one abnormal haematological parameter was 95.1% (794/835) on the first presentation to the hospital. After adjusting of age and gender, the prevalence of any white cell abnormality was 34.7% (290/835) (5.7% leukopenia, 9.6% leucocytosis, 25.4% lymphopenia, 5.5% neutropenia, 16.4% neutrophilia, 7.3% monocytoisis, and 1.2% eosinopenia). A prevalence of 15.3% (128/835) anaemia, 9.5% (79/835) thrombocytopenia, and 4.3% (36/835) thrombocytosis was also observed. The prevalence of other abnormal blood parameters was C-reactive protein 69.5% (573/835), D dimer 57.5% (280/835), high LDH 52% (383/835), high ferritin 72.1% (452/835), high international normalized ratio 5.1% (38/835), prolonged PT 32.2%(240/835), and prolonged aPTT 35.6% (264/835). Most of these findings were more common in adults as described in Table 2.

A significant difference in the prevalence of these abnormalities was evident between the two populations as described in Table 2. The haematological abnormalities were much more prevalent in adults. Still, interestingly paediatric population had higher incidence of neutropenia (4.5% in adults vs. 12.5% in paediatrics), eosinophilia (0.4% in adults vs. 3.8% in paediatrics), and monocytosis (6.4% in adults vs. 13.5% in paediatrics) (p < 0.001).

Discussion
Multiple prior studies have established the effect of the SARS-CoV-2 on the hematopoietic system [2]. The key goal of our study was to explore some of these haematological manifestations associated with COVID-19 infection and their prevalence in our population. To the best of our knowledge, this is one of the largest and only observational studies of this region which described the haematological abnormalities at presentation while comparing these findings in adult and paediatric populations.

Adult patients formed the majority 87.5% of the patients in the study. In the adult population, most patients were males 87.4%, while 52.8% of patients were male in the paediatric population. The paediatric population had no significant comorbidities, while diabetes mellitus and hypertension were the most common comorbidities in the adult population at 27.3% and 21.5%, respectively.

In the paediatric group, most patients 49% were above the age of 3 years, while infants (below the age of 1 year) and toddlers (age 1–3 years) formed 22.1% and 28.8% of the population, respectively. All the patients in the paediatrics group had a mild infection without any mortality. Perhaps, the presence of comorbidities also contributed to mortality in adult patients.

The most common blood abnormalities at presentation were noted to be increased inflammatory makers including high ferritin (72.1%), high CRP (69.5%), high LDH (52%), followed by deranged coagulation, high dimer (57.5%), and prolonged PT (32.2%) and (aPTT 35.6%); other common findings were lymphopenia (25.4%), neutrophilia (16.4%), anaemia (15.3%), leucocytosis (9.6%), monocytoisis (7.3%). It has been proposed that COVID-19 infection causes necrosis and apoptosis of the lymphocytes due to the inflammatory cytokines. Lymphopenia has been associated with severe infection and increased mortality [12, 13].

As reported in a meta-analysis, high CRP (58.3%, 95% CI: 21.8–94.7%), high LDH (57.0%, 95% CI: 38.0–76.0), lymphopenia (43.1%, 95% CI: 18.9–67.3), and high erythrocyte sedimentation rate (41.8%, 95% CI: 0.0–92.8) were the most prevalent laboratory results. These results are comparable to our findings [12].

Cytokine storm and hyperinflammation triggered by the COVID-19 underly the pathophysiology of severe COVID-19 infection. There is evidence that monocytes and macrophages play a role in fibrotic changes in the lungs of critically ill patients. It has also been proposed that a condition similar to macrophage activation syndrome is present in patients with severe COVID-19 infec-
tion. The patient’s innate immune response has a critical role in the outcome of the infection. Perhaps, the immature immune system of the children explains the milder severity of disease in this population apart from the decreased angiotensin-converting enzyme 2 receptors compared to the adult population [13–15].

We noted a significant difference in the prevalence of these findings in adults and the paediatric population (Table 2). These abnormalities were much more common in adults compared to paediatric patients, but interestingly paediatric population tended to have a higher incidence of neutropenia ($p < 0.000$). Moreover, similarly, leucocytosis was observed in 10.9% of the adult population, while leukopenia was more evident in the paediatric population (6.7%) ($p 0.002$). The neutropenia and leukopenia noted in our study may be a reflection of congenital neutropenia syndromes which is prevalent in our population.

Lymphopenia was observed in 28.5% of the adult population and only in 3.8% of the paediatric group. The prevalence of lymphopenia was less in our studied group compared to the previously reported 63% and 83.2% in a study reported from different parts of China [4, 16]. Furthermore, comparison of these findings with data in the Middle East could not be done as data on this topic in this population were limited.

It has been observed that higher white blood cell levels, neutrophilia, lymphopenia, and lower monocyte counts could be because of superimposed bacterial infection and also because of the effect of different cytokine releases during the infection, and these findings were more prevalent in the adult population which had 12% (93/741) deaths compared to no deaths observed in the paediatric population [15, 17]. These findings of higher lymphocyte count, lower neutrophil count, and lower inflammatory markers in paediatric patients were noted in other studies. Neutrophilia has also been noted in paediatric patients with MIS-C, but we did not have any patients who developed MIS-C in our study [17].

Many studies have linked haematological findings like lymphopenia with complications and poor outcomes of COVID-19 infections. These findings can be used as markers to identify patients who might benefit from early treatment and close follow-up especially as the cases of COVID-19 rise again [16, 18].

**Limitations**

This study has several limitations as it is a retrospective study; many blood tests which were not ordered in the past like interleukin 6 which is linked to severe outcomes could not be studied. None of the paediatric patients had a severe COVID-19 infection, so no correlation between the laboratories and severity of infection could be studied.

**Conclusion**

Like most viral infections, SARS-CoV-2 infection affects the immune system of the body and generates an inflammatory response which can be detected on simple routine blood tests. Many of these findings like lymphopenia, neutrophilia, and high inflammatory markers have been linked to severe COVID-19 infections and worse outcomes for the patients. These abnormalities were prevalent in the adult population, and some findings like neutropenia were more common in the paediatric population likely reflecting congenital/benign neutrophil disorders in the population and different immune responses leading to lesser inflammation and damage. We recommend further studies to compare the difference and clinical significance in haematological manifestations with different COVID-19 variant strains to identify patients prone to worse outcomes who might benefit from earlier treatment.

**Acknowledgments**

The authors would like to thank and acknowledge all valuable support from Zoubia Mohamed, Sally Awad Mohamed Rahma, Harshitha Janardhan, Lana G. Adra, Maymona Motasim Mohammad, Rommana Mehdi, Anam Ahsan, Diary Mohammad, and Marwan Zidan.

**Statement of Ethics**

The research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was taken from Dubai Scientific Research Ethics Committee (DSREC) Number DSREC/RRP/2020/22, dated August 30, 2020. Consent was taken from patients as a part of general informed consent signed on admission to Dubai Health Authority which states de-identified data can be used for research and the study was conducted maintaining full patient confidentiality.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare. The authors report no relationships that could be construed as a conflict of interest.
Funding Sources
No funding was received for this study.

Author Contributions
Saubia Fathima and Laila Al Dabal are responsible for conception and design of the study; data analysis and interpretation were done by Saubia Fathima and Salma Rahma. Saubia Fathima, Farah Chughtai, and Salma Rahma drafted and revised the final article. All authors read and approved the final draft of the manuscript.

Data Availability Statement
The data that support the findings of this study are not publicly available as data were collected from patients’ electronic medical record and can compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

References
1. Debuc B, Smadja DM. Is COVID-19 a new hematologic disease? Stem Cell Rev Rep. 2021;17(1):4–8.
2. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2020 [cited 2022 Jun 26];50(1):72–81.
3. Bohn MK, Yousef P, Steele S, Sepiashvili L, Adeli K. MultiInflammatory syndrome in children: a view into immune pathogenesis from a laboratory perspective. J Appl Lab Med. 2022 [cited 2022 Jun 26];7(1):311–21.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 [cited 2022 Jun 26];395(10223):497–506.
5. Cui X, Zhao Z, Zhang T, Guo W, Guo W, Zheng J, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). J Med Virol. 2021 Feb [cited 2022 Aug 17];93(2):1057–69.
6. Toba N, Gupta S, Ali AY, ELSaban M, Khamsi AH, Ho SB, et al. COVID-19 under 19: a meta analysis. Pediatr Pulmonol. 2021;56(6):1332–41.
7. Commissioning medicines for children in specialised services [Internet]. National Health Science: UK. [cited 2022 Jun 26]. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf.
8. Sandler SG. Primary hematology. Tefferi A, editor. Totowa, NJ: Humana Press; 2001. p. 472. $125. Hardcover. Transfusion. 2001;41(6):850.
9. Lab values, normal adult [Internet]. Medscape.com. 2021 [cited 2022 Jun 26]. Available from: https://emedicine.medscape.com/article/2172316-overview.
10. Orkin SH, Nathan DG, Ginsburg D, Look AT, Fisher DE, Lux SE. Nathan and oski’s hematology and oncology of infancy and childhood. 8th ed. London, England: W B Saunders; 2014. 2 Volume Set.
11. Berg J. The UK pathology harmony initiative; The foundation of a global model. Clin Chim Acta. 2014;432:22–6.
12. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalar-Antenezia JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Trav Med Infect Dis. 2020 Mar 13;34:101623.
13. Umakanthan S, Sahu P, Ranade AV, Bukelo MM, Rao JS, Abrahao-Machado LF, et al. Origin, transmission, diagnosis and management of coronavirus disease 2019 (COVID-19). Postgrad Med J. 2020;96(1142):753–8.
14. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020;20(6):355–62.
15. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol. 2021;191(1):4–17.
16. Liao D, Zhou F, Luo L, Xu M, Wang H, Xia J, et al. Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. Lancet Haematol. 2020 [cited 2022 Jun 26];7(9):e671–8.
17. Kaberdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021;41(1):19–32.
18. Akbari H, Tabrizi R, Lankarani KB, Aria H, Vakili S, Asadian F, et al. The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Life Sci. 2020;258(118167):118167.