Haematological parameters predicting cardiac involvement in children with COVID-19 infection

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Aim: Haematological parameters obtained from the full blood count, such as neutrophil-to-lymphocyte ratio (NLR), are cost-effective tests which have been shown to be predictive of the prognosis of many diseases. We aimed to evaluate certain haematological parameters and cardiac biomarkers to test whether they could predict cardiac involvement by COVID-19 infection.

Methods: This retrospective study included patients aged 1 month to 18 years having a positive COVID-19 PCR test but no comorbidity, who were admitted to the paediatric emergency department between 15 March 2020 and 1 February 2021.

Results: There were 292 COVID-19 PCR-positive patients, 12 MIS-C patients and 70 healthy controls. A receiver operator characteristic curve analysis was performed to predict MIS-C in patients with COVID-19 infection. An NLR value of ≥5.03 could predict MIS-C with a sensitivity of 66.7% and a specificity of 91.6%; a proBNP value of ≥329.5 ng/L with a sensitivity of 91.7% and a specificity of 95.6%; a CKMB value of ≥2.95 μg/L with a sensitivity of 100% and a specificity of 77.7%; and a troponin-I value of ≥0.03 μg/L with a sensitivity of 75% and a specificity of 99.2%. A logistic regression analysis showed that an NLR value of ≥5.03 increased the risk of MIS-C 19.3 fold; a proBNP value of ≥329.5 ng/L increased the risk 238 fold; and a troponin-I value of ≥0.03 μg/L increased the risk 60 fold.

Conclusions: At the time of admission, parameters such as proBNP, troponin-I and NLR can predict the development of MIS-C in COVID-19 patients with high sensitivity and specificity.

Key words: children; COVID-19; NLR; proBNP; troponin-I.

What is already known on this topic
1 Full blood count is a cost-effective test.
2 It has been reported that the neutrophil/lymphocyte ratio (NLR) predicts prognosis in many diseases.
3 MIS-C, a post-COVID-19 complication, can be severe.

What this paper adds
1 Parameters such as NLR, proBNP, troponin-I and CRP were shown to have high sensitivity and specificity (66.7% and 91.8%; 91.7% and 95.6%; 75% and 99.2%; 91.7% and 89.7%, respectively) in the early detection of MIS-C.
2 It will be easier for clinicians to predict the development of MIS-C in patients with COVID-19 infection.

Although more than 1 year has passed, we still continue to experience the negative effects of COVID-19, which was declared a pandemic on 11 March 2020.1 According to WHO data, 126 697 603 cases were confirmed world-wide as of 29 March 2021, and approximately 2% of these cases have died.2 Although it was initially reported that children usually survive the disease with mild or even no symptoms unlike adult patients, a multisystem inflammatory syndrome (MIS-C) associated with COVID-19 was identified in children in late April 2020.3–5 It has been reported that this syndrome possesses similar characteristics with several diseases such as Kawasaki disease and hemophagocytic lymphohistiocytosis; it is reportedly a hyperinflammatory condition with fever, increased laboratory markers of inflammation, multisystemic organ involvement and cardiovascular shock.6 MIS-C is a syndrome of post-infectious immune dysregulation. Cytokine storm plays an important role in the pathogenesis of this syndrome. Cardiac dysfunction, haematological involvement such as thrombocytopenia, coagulopathy, gastrointestinal involvement, neurological involvement and ultimately multi-organ failure may develop. Morbidity and even death may occur.7

Full blood count is a cost-effective test that can be studied in almost any health-care facility. In recent years, haematological parameters showing systemic inflammation, such as red cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR),

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Grants: None.

Conflicts of interest: None declared.

Accepted for publication 23 August 2022.
platelet-to-lymphocyte ratio (PLR), have been reported to predict prognosis in many diseases.\(^6\)\(^-\)\(^10\)

In our study, we aimed to predict COVID-19’s cardiac involvement using these cost-effective haematological parameters and to evaluate the correlation of MIS-C with these cardiac biomarkers.

**Methods**

Patients aged between 1 month and 18 years who presented to the paediatric emergency department with suspected COVID-19 between 15 March 2020 and 1 February 2021 were included in this single-centre, retrospective study.

Almost everyone in Turkey can present to the emergency departments. There are no restrictions as to which patients can present to the emergency departments ‘green zone’.\(^11\)\(^-\)\(^13\) Therefore, patients with low, moderate, and severe risk were included in our study.

This study was conducted in accordance with the criteria of Declaration of Helsinki. Its ethics approval was obtained from the local ethics committee before the start of the study (2021/10-03). Healthy children of the same age without complaints were included as the control group. Patients whose haematological parameters and cardiac biomarkers were missing, patients with comorbid conditions (patients with cardiac or neurological sequelae, asthma, immunodeficiency, haematological disorders or malignancy), and patients with a negative COVID-19 PCR test were excluded from the study.

The demographic characteristics, and clinical and laboratory findings at the time of admission (full blood count parameters, pro-brain natriuretic peptide (proBNP), creatine kinase, CK-MB and troponin-I) were obtained from the medical records of the study subjects.

MIS-C was diagnosed according to the diagnostic criteria issued by the Center for Disease Control and Prevention (CDC). These include age < 21 years, fever ≥38°C for ≥24 h, laboratory evidence of inflammation, serious illness requiring hospitalisation, involvement of two or more systems, positive PCR, serology, or antigen tests, COVID-19 exposure within 4 weeks before symptom onset, and the absence of any other possible cause.\(^3\)

Nasopharyngeal swabs for COVID-19 RT-PCR analysis were examined using the BIO-RAD CFX96 Real-Time System C1000 Touch Thermal Cycler Device, SARS-CoV-2 Double Gene RT-qPCR 1000 Rxn kit and COVID-19 RT-PCR kit.

The Statistical Package for the Social Sciences for Windows 22 software was used for statistical analysis. Study variables were presented as number (%) – percentage (%) and mean ± standard deviation. The normality of distribution of the study variables was tested with the Kolmogorov–Smirnov test. Normally distributed numerical variables were compared by one-way analysis of variance or Student’s t-test while non-normally distributed ones were compared by the Kruskal–Wallis test or Mann–Whitney U test. The risk factors were evaluated with univariate and multivariate logistic regression models. The variables found to be significantly predictive of MIS-C in the univariate analysis were included in the logistic regression analysis. The receiver operator characteristic (ROC) curve analysis was performed to find an optimal cutoff point of candidate variables for the prediction of MIS-C. A \(P\) value of less than 0.05 was considered statistically significant.

**Results**

Between 15 March 2020 and 1 February 2021, a total of 2870 COVID-19 tests were performed on patients who were admitted to the paediatric emergency service with suspected COVID-19 infection. A total of 2784 patients underwent COVID-19 PCR testing; 32 COVID-19 patients underwent IgM rapid testing; 43 patients underwent COVID-19 IgG rapid testing, and 11 - underwent both COVID-19 IgM and IgG rapid testing. According to the inclusion criteria, 292 patients with positive COVID-19 PCR tests, 12 MIS-C patients and 70 healthy controls were included in this study.

The mean age of the patients was \(11.04 \pm 5.34\) (0–18) years. The mean age of the 70 healthy controls was \(11.41 \pm 4.92\) years; 292 patients with COVID-19 infection who had a positive COVID-19 PCR test but no MIS-C had a mean age of \(10.89 \pm 5.53\) years; and 12 patients with MIS-C had a mean age of \(8.35 \pm 5.32\) years. There was no statistically significant difference between the groups in terms of age and gender (\(P = 0.273, P = 0.479\), respectively).

When the patients were evaluated according to their symptoms, the most common symptoms were fever (56.8%), cough (31.5%), weakness (15.8%) and sore throat (18.2%). The least common symptoms were loss of appetite (1.7%) and nausea (3.1%).

Abdominal pain was present in 50% of MIS-C patients and vomiting in 35% of them; both rates were significantly higher than those of the COVID-19 cases without MIS-C (\(P < 0.001, P = 0.003\), respectively) (Table 1).

When the patients were evaluated according to laboratory data; WBC, CRP, procalcitonin, IG (immature granulocyte), IG%, NLR, troponin-I and proBNP levels were significantly higher in the MIS-C group compared to the other groups (\(P = 0.005, P < 0.001, P < 0.001, P < 0.001, P < 0.001, P < 0.001, P < 0.001\), respectively). The albumin level was significantly lower in the MIS-C group (\(P < 0.001\)). There was no statistically significant difference between the groups regarding creatine kinase and CKMB levels (\(P = 0.066, P = 0.051\), respectively) (Table 2).

The laboratory data of the patients were analysed with a ROC curve to predict MIS-C (Table 3). The best cutoff points for MIS-C were determined. According to these analyses, in patients with suspected COVID-19 infection; MIS-C can be predicted by CRP levels of ≥12.65 mg/L, with a sensitivity of 91.7% and specificity of 89.7%; by an IG level of ≥35.10⁶/L with a sensitivity of 58.3% and a specificity of 88.7%; by an IG% level of ≥0.35 with a sensitivity of 73.7% and a specificity of 88.7%; by a neutrophil-to-lymphocyte ratio (NLR) level of ≥5.03 with a sensitivity of 66.7% and a specificity of 91.6%; by a procalcitonin level of ≥0.165 μg/L with a sensitivity of 100% and a specificity of 93.4%; by a proBNP level of ≥329.5 ng/L with a sensitivity of 91.7% and a specificity of 95.6%; by a CKMB level of ≥2.95 μg/L with a sensitivity of 100% and a specificity of 77.7%; and by a troponin-I level of ≥0.03 μg/L with a sensitivity of 75% and specificity of 99.2%.

In addition, when a risk analysis was performed with logistic regression analysis according to the cutoff values of the laboratory data, using a ROC curve analysis for MIS-C development, we determined that if IG was ≥35.10⁶/L, the risk...
was 15.63 times higher, if IG% was ≥0.35, the risk was 11 times higher; if the NLR was ≥5.03, the risk was 19.3 times higher, if procalcitonin was ≥0.165 μg/L, the risk was 7.5 times higher, if proBNP was ≥329.5 ng/L, the risk was 238 times higher, if troponin-I was ≥0.03 μg/L, the risk was 60 times higher; and if CRP was ≥12.65 mg/L, the risk was 142 times higher (Table 4).

When the patients were evaluated according to the correlation of laboratory findings, there was a weak positive correlation between proBNP and IG (r: 0.206, P < 0.001), a moderate positive correlation between proBNP and troponin-I (r: 0.519, P < 0.001), a moderate positive correlation between proBNP and CRP (r: 0.510, P < 0.001), a moderate positive correlation between proBNP and

### Table 1 Comparison of patients according to their demographic characteristics and symptoms

| Healthy control (n = 70) | Non-MIS-C (n = 292) | MIS-C (n = 12) | P† |
|-------------------------|---------------------|----------------|----|
| Age (mean ± SD)         | 11.41 ± 4.92        | 10.89 ± 5.53   | 8.35 ± 5.32 | 0.273 |
| Gender                  | N (%)               | N (%)          | N (%)      | P‡ |
| Male                    | 34 (48.6)           | 143 (49)       | 4–33.3     | 0.479 |
| Female                  | 36 (51.4)           | 149 (51)       | 8 (66.7)   |    |
| Symptoms                |                     |                |            |    |
| Fever                   | –                   | 166 (56.8)     | 12 (100)   | 0.003 |
| Cough                   | –                   | 92 (31.5)      | 1 (8.3)    | 0.088 |
| Diarrhoea               | –                   | 24 (8.2)       | 2 (16.7)   | 0.305 |
| Loss of taste           | –                   | 20 (6.8)       | 0          | 0.348 |
| Loss of smell           | –                   | 23 (7.9)       | 0          | 0.312 |
| Myalgia                 | –                   | 16 (5.5)       | 0          | 0.405 |
| Loss appetite           | –                   | 5 (1.7)        | 1 (8.3)    | 0.108 |
| Weakness                | –                   | 53 (18.2)      | 1 (8.3)    | 0.383 |
| Vomiting                | –                   | 14 (4.8)       | 3 (25)     | 0.003 |
| Abdominal pain          | –                   | 15 (5.1)       | 6 (50)     | <0.001 |
| Headache                | –                   | 46 (15.8)      | 2 (16.7)   | 0.932 |
| Nausea                  | –                   | 9 (3.1)        | 1 (8.3)    | 0.319 |
| Runny nose              | –                   | 15 (5.1)       | 2 (16.7)   | 0.140 |
| Throat ache             | –                   | 53 (18.2)      | 0          | 0.104 |

‡ Independent Student’s t-test. MIS-C, multisystem inflammatory syndrome.

### Table 2 Comparison of patients’ laboratory data

| Healthy control (n = 70) | COVID-19 infected patients (n = 304) |
|-------------------------|-------------------------------------|
| WBC (10^9/L)            | Mean ± SD                           |
| 7.906 ± 2.058           | Mean ± SD                           |
| 6.947 ± 2.685           | 8.462 ± 2.415                       | 0.005 |
| CRP (mg/L)              | Mean ± SD                           |
| 3.139 ± 0.336           | 6.341 ± 10.299                      | 154.041 ± 113.142 | <0.001 |
| Procalcitonin (μg/L)    | 0.034 ± 0.017                       | 0.082 ± 0.123      | 9.404 ± 12.399 | <0.001 |
| Albumin (g/dL)          | 4.783 ± 0.226                       | 4.721 ± 0.264      | 3.257 ± 0.466 | <0.001 |
| IG (10^6/L)             | 15.14 ± 9.74                        | 16.45 ± 16.54      | 39.17 ± 28.11 | <0.001 |
| IGX                     | 0.178 ± 0.112                       | 0.221 ± 0.175      | 0.433 ± 0.270 | <0.001 |
| NLR                     | 1.37 ± 0.96                         | 2.37 ± 2.59        | 7.43 ± 5.61  | <0.001 |
| CK (U/L)                | 129.25 ± 98.89                      | 109.19 ± 78.79     | 77.67 ± 58.84 | 0.066 |
| CKMB (μg/L)             | 5.97 ± 17.47                        | 2.76 ± 2.08        | 3.92 ± 4.75  | 0.051 |
| Troponin-I (μg/L)       | 0.00 ± 0.00                         | 0.0013 ± 0.0107    | 0.037 ± 0.0674 | <0.001 |
| ProBNP (ng/L)           | 50.70 ± 35.49                       | 99.78 ± 210.71     | 6855.25 ± 6110.70 | <0.001 |

† Kruskal–Wallis test. CK, creatine kinase; CRP, C-reactive protein; IG, immature granulocyte; MIS-C, multisystem inflammatory syndrome in children; NLR, neutrophil-to-lymphocyte ratio; ProBNP, pro-brain natriuretic peptide.
procalcitonin ($r: 0.457, P < 0.001$), but no significant correlation between proBNP and CKMB ($r: 0.028, P = 0.682$) (Table 5).

The clinical data of 12 patients followed up with the diagnosis of MIS-C are shown in Table 6. All patients were given intravenous immunoglobulin (IVIG) and steroid. Only

### Table 3: Determination of cutting points of laboratory data that can predict MIS-C

| Cutoff value | AUC   | Sensitivity | Specificity | Asymptotic 95% confidence interval |
|--------------|-------|-------------|-------------|-----------------------------------|
| CRP (mg/L)  | ≥12.65 | 0.907       | 0.917       | 0.897                              |
| IG (≥35–10^9/L) | ≥35   | 0.749       | 0.583       | 0.918                              |
| IG%          | ≥0.35  | 0.737       | 0.583       | 0.887                              |
| NLR          | ≥5.03  | 0.823       | 0.667       | 0.916                              |
| Procalcitonin (μg/L) | ≥0.165 | 0.992       | 1           | 0.934                              |
| ProBNP (ng/L) | ≥329.5 | 0.980       | 0.917       | 0.956                              |
| CK-MB (μg/L) | ≥2.95  | 0.897       | 1           | 0.777                              |
| Troponin-I (μg/L) | ≥0.03  | 0.870       | 0.750       | 0.992                              |

† ROC curve analysis. CK, creatine kinase; CRP, C-reactive protein; IG, immature granulocyte; MIS-C, multisystem inflammatory syndrome in children; NLR, neutrophil-to-lymphocyte ratio; ProBNP, pro-brain natriuretic peptide; ROC, receiver operator characteristic.

### Table 4: Evaluation of risk factors for MIS-C development by logistic regression analysis

| OR         | 95% CI          | P‡  | Risk |
|------------|-----------------|-----|------|
| IG (≥35–10^9/L)  | 15.63           | 6.103–53.02 | <0.001 | Yes |
| IG % (≥0.35)    | 11              | 3.298–36.607 | <0.001 | Yes |
| NLR (≥5.03)     | 19.3            | 5.522–67.417 | <0.001 | Yes |
| Procalcitonin (≥0.165 μg/L) | 7.5              | 4537.12–550 | <0.001 | Yes |
| ProBNP (≥329.5 ng/L) | 238             | 28.909–1957.300 | <0.001 | Yes |
| CK-MB (≥2.95 μg/L) | 0.263           | 0.076–0.909 | 0.035 | No |
| Troponin-I (≥0.03 μg/L) | 60              | 8.907–404.190 | <0.001 | Yes |
| CRP (≥12.65 mg/L) | 142            | 17.660–1144.291 | <0.001 | Yes |

† Logistic regression analyses. CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; IG, immature granulocyte; MIS-C, multisystem inflammatory syndrome in children; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; ProBNP, pro-brain natriuretic peptide.

### Table 5: Correlations between patients' laboratory data

|         | IG                | ProBNP              | Troponin-I       | CKMB            | CRP             | Procalcitonin |
|---------|-------------------|---------------------|------------------|-----------------|-----------------|---------------|
| Pearson correlation | 1 | 0.206†          | 0.067            | 0.012           | 0.398†          | 0.223†        |
| P       | 0.000             | 0.225              | 0.866            | 0.000           | 0.000           |
| Pearson correlation | 0.206†     | 1                 | 0.519†           | 0.028           | 0.510†          | 0.457†        |
| P       | 0.000             | 0.000              | 0.682            | 0.000           | 0.000           |
| Pearson correlation | 0.067   | 0.519†           | 1                | 0.027           | 0.155†          | 0.321†        |
| P       | 0.225             | 0.000              | 0.693            | 0.005           | 0.000           |
| Pearson correlation | 0.012   | 0.028            | 0.027            | 1               | −0.027          | −0.026        |
| P       | 0.866             | 0.682              | 0.693            | 0.692           | 0.724           |
| Pearson correlation | 0.398†     | 0.510†            | 0.155†           | −0.027          | 1               | 0.536†        |
| P       | 0.000             | 0.000              | 0.005            | 0.692           | 0.000           |
| Pearson correlation | 0.223†   | 0.457‡           | 0.321†           | −0.026          | 0.536†          | 1             |
| P       | 0.000             | 0.000              | 0.000            | 0.724           | 0.000           |

† Correlation is significant at the 0.01 level (two-tailed). CK, creatine kinase; CRP, C-reactive protein; IG, immature granulocyte; MIS-C, multisystem inflammatory syndrome in children; ProBNP, pro-brain natriuretic peptide.
Table 6  The clinical data of 12 patients with MIS-C

| Patient number | Age    | Sex | MIS-C severity | Vasoactive drugs       | Hospital stay (day) | First echo                  | Cardiac dysfunction findings                                      |
|----------------|--------|-----|----------------|------------------------|---------------------|-----------------------------|-------------------------------------------------------------------|
| 1              | 8 years| Female | Severe         | Dobutamin 5 days       | 22                  | Ef 64                       | Tachycardia, Prolonged capillary refilling time                    |
|                |        |       |                |                        |                     | Kf 34                        | Lightly confused, Abdominal pain                                 |
|                |        |       |                |                        |                     | Trace MR                     |                                                                   |
| 2              | 7 years| Male  | Severe         | Total 11 days Dobutamin 8 days Adrenalin 6 days Milrinon 7 days | 46                  | Ef 62                       | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 32                        | Clounding of consciousness                                        |
|                |        |       |                |                        |                     | Mild MR                      |                                                                   |
|                |        |       |                |                        |                     |                             | Prolonged capillary refilling time                                |
| 3              | 14 years| Male  | Moderate       | Dobutamin 3 days       | 9                   | Ef 62                       | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 33                        | Abdominal pain, Abdominal pain                                   |
|                |        |       |                |                        |                     | Mild MR                      | Prolonged capillary refilling time                                |
|                |        |       |                |                        |                     |                             | Tachycardia                                                      |
| 4              | 2 months| Male  | Severe         | Dobutamin 8 days       | 19                  | Ef 71 (while administering dobutamine) Kf 38 | Tachypnea, Tachycardia, inability to feed, Prolonged capillary refilling time |
|                |        |       |                |                        |                     |                             | Abdominal pain                                                   |
|                |        |       |                |                        |                     |                             | Hypotension                                                       |
|                |        |       |                |                        |                     |                             | Tachycardia                                                      |
|                |        |       |                |                        |                     |                             | Tachypnea                                                        |
| 5              | 13 years| Male  | Severe         | Dobutamin 6 days       | 20                  | Ef 38                       | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 19                        | Abdominal pain                                                   |
|                |        |       |                |                        |                     | Trace AR                     | Hypotension                                                       |
|                |        |       |                |                        |                     | Mild MR                      | Tachycardia                                                      |
| 6              | 1 month | Female | Moderate      | Dobutamin 11 days      | 21                  | Ef 74                        | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 40                        | Prolonged capillary refilling time                                |
| 7              | 6.5 years| Male  | Moderate       | Dobutamin 3 days       | 20                  | Ef 71                        | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 39                        | Prolonged capillary refilling time                                |
|                |        |       |                |                        |                     | Mild MR, Trace AR            | Abnormality of feeding, Prolonged capillary refilling time        |
| 8              | 12 years| Female | Moderate      | Dobutamin 6 days       | 12                  | Ef 62                        | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 33                        | Prolonged capillary refilling time                                |
|                |        |       |                |                        |                     | Mild MR                      | Abnormality of feeding                                            |
| 9              | 2.4 years| Male  | Moderate       | Dobutamin 9 days       | 15                  | Ef 76                        | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 43                        | Prolonged capillary refilling time                                |
|                |        |       |                |                        |                     | Pericardial effusion 3 mm at systole | Abnormality of feeding, Prolonged capillary refilling time        |
| 10             | 5.4 years| Male  | Mild           | No                      | 7                   | Ef 70, Kf 39                 | --                                                                |
| 11             | 13 years| Male  | Moderate       | Dobutamin 5 days       | 19                  | Ef 71                        | Tachycardia                                                      |
|                |        |       |                |                        |                     | Kf 40                        | Abdominal pain                                                   |
|                |        |       |                |                        |                     |                             | Prolonged capillary refilling time                                |
| 12             | 8 years | Female | Severe         | Dobutamin 3 days Adrenalin 2 days Milrinon 3 days | 14                  | EF: 44                       | Hypotension                                                       |
|                |        |       |                |                        |                     | KF:22                        | Hepatomegaly                                                    |
|                |        |       |                |                        |                     | Mild MR, Pericardial effusion 6 mm at systole, 1 mm at diastole | Tachypnea                                                        |

AR, aortic regurgitation; Ef, ejection fraction; MR, mitral regurgitation; SF, shortening fraction.
patients have multisystem symptoms such as shock, cardiac dysfunction, and abdominal pain. In a European study involving 286 MIS-C patients, Valverde et al. reported that cardiac involvement was frequent, and the levels of BNP, ferritin, D-dimer, troponin, CRP, and procalcitonin were increased. Although MIS-C is characterised by multisystemic involvement, its mortality is reportedly low in children compared with adults. In a review by Hoste et al., BNP and troponin levels indicating cardiac damage as well as inflammatory markers such as CRP, ferritin and IL-6 increased in MIS-C cases.

Although WBC increased mostly, lymphocytopenia was widely observed. Platelet counts were found to be normal, D-dimer and fibrinogen were increased in coagulation parameters. Similarly, in a study reported by Minocha et al., CRP, D-dimer and ferritin levels were increased in MIS-C patients. Cardiac abnormalities were reported in 73% of the patients. Increased BNP was seen in 43% of these, and an increased troponin level in 21%. In a case series of 1116 patients, Feldstein et al. reported a higher neutrophil to lymphocyte ratio, CRP, and a lower platelet count in patients with MIS-C compared with patients with COVID-19. In our study, we found a significantly higher NLR level in the MIS-C group, which was consistent with the results reported by Feldstein et al. In addition, in contrast to the literature, we determined a cutoff value for NLR that can predict MIS-C (66.7% sensitivity, 91.6% specificity for an NLR level ≥ 5.03). We also showed that an NLR level ≥ 5.03 increased the risk of developing MIS-C approximately 19 times. Hypoalbuminemia has been frequently reported in patients with MIS-C. Consistent with the literature, we found that albumin levels were significantly lower in the MIS-C group (P < 0.001).

In a review by Kwak et al., higher procalcitonin levels were found in MIS-C patients compared with COVID-19 patients. While neutrophilia and lymphopenia were observed in most patients, anaemia and thrombocytopenia were only observed in some of them. However, another study showed neutrophilia, lymphopenia, and high levels of CRP, fibrinogen and D-dimer in children with MIS-C. Troponin-I was also found to be moderately high, while BNP was significantly higher in those children.

In our study, in accordance with the literature, we found significantly higher WBC, CRP, procalcitonin, NLR, troponin-I, and proBNP levels in the MIS-C group compared with patients with COVID-19 infection but without MIS-C, and the healthy controls. Unlike previous studies, we determined the sensitivity and specificity of these parameters according to the cutoff values that can predict MIS-C, and we also made a risk analysis according to these cutoff values. According to these analyses, we showed that a procalcitonin level ≥ 0.165 μg/L increased the risk of MIS-C by 7.5 times; a proBNP level ≥ 329.5 ng/L likewise increased the same risk by 238 times; a troponin-I level ≥ 0.03 μg/L increased the risk by 60 times; and a CRP level ≥ 12.65 mg/L increased the risk by 142 times. Moreover, in contrast to the literature, we performed correlation analyses to evaluate the relationship between proBNP, procalcitonin, CRP, CK-MB and troponin-I. Based on this analysis, we found a moderate positive correlation between proBNP and CRP, and procalcitonin. This is meaningful in that it shows us that as the inflammation increases, the heart is more likely to be affected.

Discussion

Our study is one of the rare studies in the literature that examines blood parameters that can shed light on cardiac involvement and prognosis in paediatric patients with COVID-19, and it analyses the sensitivity, specificity, and the relative risk of these parameters for the development of MIS-C. According to our results, a proBNP level of 329.5 ng/L or above and a procalcitonin value of 0.165 μg/L or above at the time of admission could predict MIS-C with sensitivities and specificities of more than 90%.

Although the pathophysiology of MIS-C has not yet been fully elucidated, it has been proposed that it occurs due to immune dysregulation. Patients have multisystemic symptoms such as shock, cardiac dysfunction, and abdominal pain. In a European study involving 286 MIS-C patients, Valverde et al. reported that cardiac involvement was frequent, and the levels of BNP, ferritin, D-dimer, troponin, CRP, and procalcitonin were increased. Although MIS-C is characterised by multisystemic involvement, its mortality is reportedly low in children compared with adults. In a review by Hoste et al., BNP and troponin levels indicating cardiac damage as well as inflammatory markers such as CRP, ferritin and IL-6 increased in MIS-C cases.

While neutrophilia and lymphopenia were observed in most patients, anaemia and thrombocytopenia were only observed in some of them. However, another study showed neutrophilia, lymphopenia, and high levels of CRP, fibrinogen and D-dimer in children with MIS-C. Troponin-I was also found to be moderately high, while BNP was significantly higher in those children.

In our study, in accordance with the literature, we found significantly higher WBC, CRP, procalcitonin, NLR, troponin-I, and proBNP levels in the MIS-C group compared with patients with COVID-19 infection but without MIS-C, and the healthy controls. Unlike previous studies, we determined the sensitivity and specificity of these parameters according to the cutoff values that can predict MIS-C, and we also made a risk analysis according to these cutoff values. According to these analyses, we showed that a procalcitonin level ≥ 0.165 μg/L increased the risk of MIS-C by 7.5 times; a proBNP level ≥ 329.5 ng/L likewise increased the same risk by 238 times; a troponin-I level ≥ 0.03 μg/L increased the risk by 60 times; and a CRP level ≥ 12.65 mg/L increased the risk by 142 times. Moreover, in contrast to the literature, we performed correlation analyses to evaluate the relationship between proBNP, procalcitonin, CRP, CK-MB and troponin-I. Based on this analysis, we found a moderate positive correlation between proBNP and CRP, and procalcitonin. This is meaningful in that it shows us that as the inflammation increases, the heart is more likely to be affected.

Conclusion

Our study is a valuable one because it provided cutoff values, sensitivity-specificity levels, and a risk analysis to predict MIS-C using several laboratory parameters; furthermore, it also involved low-risk patients. Parameters such as proBNP, troponin-I, NLR and CRP were shown to have high sensitivities and specificities for the early detection of MIS-C. These findings will make it easier for clinicians to predict the development of MIS-C in patients with suspected COVID-19 infection.

Limitation

The limitations of our study include its non-prospective, single-centre and small-volume design.

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