Coronary Aneurysm and IVIG Resistance Prediction in Kawasaki Disease

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Research article

Keywords: Kawasaki disease, prolonged fever, coronary aneurysm, IVIG resistance

Posted Date: August 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56396/v1

Abstract

Background: Kawasaki disease (KD) is the most common cause of coronary artery aneurysm (CAA) in children. This study aimed to determine the clinical characteristics, demographic features, frequency of coronary involvement, and resistance to intravenous immunoglobulin (IVIG) treatment in Turkey based on our data.

Methods: Patients with KD were evaluated with demographic data, clinical, laboratory, and echocardiographic findings.

Results: Between 2010–2019, a total of 259 patients (male/female: 1.67) were treated in our hospital, with 48 (%19) cases < 1 year of age. According to diagnostic criteria, 31% were diagnosed with typical KD and 69% with atypical (incomplete) KD. The frequency of clinical findings were as follows: changes in the lips and oral mucosa (79%); polymorphic rash (69%); conjunctivitis (65%); changes in the extremities (54%); and cervical lymphadenopathy (48%). There was no significant difference between typical and atypical KD in the frequency order. CAA development and IVIG resistance occurred in 11.6% and 12.3% of cases, respectively. IVIG resistance was more common in infants and hospitalization times were longer in this group. Coronary artery lesions existed in 45 patients; right coronary artery (RCA) alone (20%), left coronary artery (LCA) alone (44.5%), and RCA and LCA together were involved (35.5%). The left main coronary artery affected 20 patients, the left anterior descending artery (LAD) affected nine patients (45%), the left circumflex artery (LCx) affected two patients (10%), and the LAD and LCx together affected two patients (10%). None of the patients had myocardial infarctions or died during follow-up.

Conclusion: KD is a systemic vasculitis common in pediatric infants in which coronary artery involvement affects prognosis. Due to IVIG resistance and increased coronary involvement accompanying this vasculitis, it is an important problem in countries where the disease is common. It is important to know the factors that increase the risk of coronary involvement and IVIG resistance development.

Background

Kawasaki disease (KD) is an acute febrile systemic vasculitis of childhood that is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rashes, and cervical lymphadenopathy.[1-3]

KD generally in children < 5 years of age, and if left untreated it has been reported that 15%–25% of patients with KD develop coronary artery lesions ([CALs], aneurysms, or ectasia).[3] KD can cause myocarditis, arrhythmias, and myocardial infarction in the acute phase, and sudden cardiac death due to coronary artery aneurysms and stenosis in the subacute and chronic phases. KD is an important health problem, and early diagnosis and treatment significantly reduce the risk of complications, morbidity, and mortality with coronary artery disease.[1-4]

Laboratory tests, although non-specific, provide support for a diagnosis of KD in patients with non-classic, but suggestive clinical features. Clinical experience suggests that KD is unlikely if the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count are normal after day 7 of illness. In addition, a low white blood cell count and lymphocyte predominance suggest an alternative diagnosis.[2]

The efficacy of intravenous immunoglobulin (IVIG) administered in the acute phase of KD has been well-established to reduce the prevalence of coronary artery abnormalities. Patients who laboratory evidence of inflammation who fail to respond to a second infusion of IVIG, steroids, or infliximab require additional therapy to control inflammation.[2-4]

In this study we determined the clinical characteristics, laboratory findings, demographic features, frequency of coronary involvement, and resistance to IVIG treatment in Turkey based on the data from our hospital.

Methods

The diagnosis of KD is of two types (classical type/complete KD and incomplete KD/atypical KD).[2] The diagnosis of typical KD is based on the presence of ≥ 5 days of fever and the presence of ≥ 4 of 5 principal clinical features.[2] The diagnosis of incomplete (atypical) KD should be considered in any infant or child with prolonged unexplained fever, < 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings.[2]

Gender, age at diagnosis, presence of diagnostic criteria, number of days with fever, and personal and family histories were recorded. Twenty-six cases with missing file data or with a diagnosis difference other than KD were excluded from the study at the beginning.

The patients were subjected to echocardiographic examination at the time of diagnosis and in the subacute period for the presence of coronary artery involvement and the risk of complications. Myocardial wall mobility, ejection fraction values (%), and the diameters of coronary arteries were measured; Z scores were calculated according to American Heart Association (AHA) guidelines.[2]

According to the Z score calculation, the following definitions were applied: dilation, 2 < Z score < 2.5 or if initially < 2 and a decrease in Z score during follow-up ≥1; small aneurysm, 2.5 ≤ Z score < 5; moderate aneurysm, 5 ≤ Z score < 10; and large or giant aneurysm, Z score was defined as ≥ 10.[2]

IVIG and aspirin were given in appropriate doses to all patients hospitalized with a diagnosis of KD according to AHA criteria as the standard primary treatment.[2] IVIG resistance is defined as recurrent or permanent fever development at least 36 h after the end of the IVIG infusion in 10%–20% of patients with KD.[2,5,6]

The cases were grouped in terms of coronary artery aneurysms (CAAs) development and responses to IVIG treatment. The gender of the patients, the age at the time of diagnosis, the presence of diagnostic

criteria, the number of days with fever, and the personal and family histories were recorded. Retrospective statistical comparisons were made between the groups.

All data were obtained from clinical and laboratory findings recorded at the time of diagnosis, echocardiographic examinations obtained at diagnosis, and follow-up. Twenty-six patients with missing file data or with a diagnosis other than KD were excluded from the study at the beginning.

Laboratory findings included hemogram parameters, ESR, acute phase reactants (CRP, procalcitonin [PCT], and ferritin), electrolytes (Na, K, Cl, Ca, Mg, and P), kidney and liver function tests (ALT, AST, GGT, LDH, albumin, ALP, total and direct bilirubin, urea, creatinine, and uric acid), lipid profiles (total cholesterol, LDL, HDL, and triglycerides), coagulation values (PT, aPTT, and INR), urinalyses, and hemoculture results.

Data were analyzed using (SPSS Statistics for Macintosh, version 24.0; IBM Corp., Armonk, NY, USA). Categorical variables were summarized using frequencies (percentage [%]). The mean ± standard deviation was used for continuous variables. Normality was assessed for continuous data using the Kolmogorov–Smirnov test. An independent samples t-test was used for continuous variables. Categorical variables were compared using a chi-squared test. A p-value < 0.05 was taken as an indicator of statistical significance. Results and significance values are summarized in the relevant tables.

Results

Two hundred fifty-nine patients (males, 162, females 97; male-to-female ratio, 1.67) were treated in our hospital, with 48 of patients (19%) < 1 year of age. The age range was 3 months–9.8 years. The average number of days before admission to the hospital was 6.7. Of the patients, 90.7% received outpatient antibiotic therapy prior to hospitalization. CAA development and IVIG resistance were noted in 11.6% and 12.3% of patients, respectively. Coronary ectasia/dilatation was detected in 15 patients (6% [2 < Z score < 2.5]), and the coronaries were completely normal in 214 patients (83%). According to the diagnostic criteria, 31% of patients were treated as typical KD and 69% as atypical (incomplete) KD. The frequency of clinical findings were as follows: changes in the lips and oral mucosa (79%); polymorphic rash (69%); conjunctivitis (65%); changes in the extremities (54%); and cervical lymphadenopathy (48%). The frequencies of clinical findings in diagnostic types are summarized in Table 1.

CALs were demonstrated in 45 patients; the right coronary artery (RCA) alone (20%), the left coronary artery (LCA) alone (44.5%), and the RCA and LCA were involved together (35.5%). The left main coronary artery (LMCA) affected 20 patients, the left anterior descending artery (LAD) affected nine patients (45%), the left circumflex artery (LCx) affected two patients (10%), and the LAD and LCx together affected two patients (10%). Of the patients with coronary artery involvement, 53.3% were < 1 year of age and 83.3% were < 5 years of age. IVIG resistance was detected in 35.6% of patients with CAAs.

All patients were treated with standard primary therapy, IVIG, and aspirin. Aspirin was discontinued in 29 patients (11%) because salicylic acid poisoning developed. Two patients were given pulsed steroid therapy, eight patients needed intensive care, and one patient was treated with plasmapheresis.

Table 2 and 3 summarize the clinical and demographic data of the patients with respect to their responsiveness to IVIG treatment and the development of CAAs. It was observed that the frequency of CAA development increased in IVIG-resistant patients, and similarly, the frequency of IVIG resistance increased in those who developed CAAs. This association was statistically significant ($p < 0.001$). There was a statistically significant difference between the age groups with both CAA development and IVIG resistance using a chi-square test and no significant difference existed as a function of gender.

When IVIG resistant and sensitive patients are compared (Table 3) 91.6% of IVIG-resistant patients were < 5 years of age. Hospitalization time and coronary artery involvement increased and were statistically significant.

Laboratory findings were analyzed by grouping in Table 4. according to coronary involvement and in Table 5 according to IVIG responsiveness. In Table 4, the laboratory findings of patients with KD were compared according to the presence of coronary artery involvement. When the laboratory findings of patients with coronary artery involvement were examined, it was found that the hematocrit, total protein, and albumin levels decreased, and the leukocyte count, platelet count, and CRP, troponin T, and N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels increased.

In Table 5, the laboratory findings of patients with IVIG resistance were compared with patients who were sensitive to IVIG. In patients with IVIG resistance, the leukocyte and platelet counts, CRP, and ALT, troponin T, and NT-proBNP levels were increased, while the hematocrit and sodium levels were decreased.

Discussion

A CAA is the most important complication of KD. CAAs develop in 15%–25% of untreated patients; this rate decreases to 5% with treatment within the first 10 days.[3]

Early diagnosis and treatment is very important because it directly affects mortality. To provide early intervention for CALs caused by KD, we analyzed the clinical characteristics of typical and incomplete KD patients. In this study there was no significant difference between the frequency of clinical findings in patients diagnosed with typical and atypical KD. The most common findings in both groups were mucosal involvement in the mouth, polymorphic exanthema, and non-exudative conjunctive injection. The most common clinical finding (80%) in some studies was non-exudative conjunctive injection followed by polymorphic exanthema and mucosal involvement in the mouth.[7] Asian patients with changes in the oral mucosa, cervical lymphadenopathy, swelling of the extremities, and polymorphous rashes were more likely to be IVIG-resistant, but in non-Asian patients there was no significant difference among these symptoms and IVIG resistance.[17] In the population in our study, we did not note any significant difference between IVIG resistance and the risk of developing coronary lesions and clinical findings.

The prevalence of coronary artery abnormalities in a clinical trial of initial treatment was 23% 4 weeks after enrollment, which reduced to 8% with 4 infusions of low-dose IVIG. In a subsequent trial of single

high-dose IVIG, this was further reduced to approximately 4%.[8,9] In our study, CAAs were detected in 11.6% of patients. There is no conclusive data regarding the incidence of the disease and complications due to the lack of large-scale research in South Korea with a sufficient number of cases. Several different risk scores are used to predict IVIG resistance and CALs. Shin et al.[10] reported that among the risk scoring systems, the Kobayashi risk score demonstrated significant differences between IVIG resistance and responder groups in Korean patients with KD.

Many researchers have scrutinized the clinical data and laboratory parameters at onset predicting the risk of CAA.[11,12] Risk factors for CAA are duration of fever > 2 weeks, platelet count, increased acute phase reactants, and age < 5 years.

Demonstration of CALs by echocardiography is important for prognostication. Damage to coronary arteries is a substantial risk for a significant percentage of children with KD, most often for those with resistance to IVIG.

Maximal efforts should be made to visualize all major coronary artery segments. In order of highest-to-lowest frequency of occurrence, typical sites of CAAs include the proximal LAD and proximal RCA, followed by the LMCA, LCx, distal RCA, and the junction between the RCA and posterior descending coronary artery. Enlargement of the LMCA caused by KD does not involve the orifice and rarely occurs without associated dilation of the LAD, the LCx, or both arteries.[2] In our study CALs existed in 45 patients; the RCA alone (20%), the LCA alone (44.5%), and the RCA and LCA were involved together (35.5%). The LMCA affected 20 patients, the LAD affected nine patients, the LCx affected two patients, and LAD and LCx together affected two patients. IVIG resistance was more common in infants and the hospitalization times were longer in this group. The coronary involvement rate in our patients was 17.3%. This rate was 12.8% in the IVIG-responsive group and 50% in the IVIG-resistant group.

KD has no specific diagnostic laboratory markers. Recent studies have investigated factors for predicting resistance to IVIG and CALs. These data include the duration of fever, polymorphonuclear neutrophil (PMN) cell count, hemoglobin level, platelet count, and CRP, transaminase, total bilirubin, and NT-proBNP, albumin, and sodium levels.[13] In our study, when the laboratory findings of the group in which coronary artery aneurysms were detected in KD, the leukocyte and platelet counts, and CRP, troponin T, and NT-proBNP levels were significantly increased and the albumin level was decreased.

Several previous studies demonstrated that a higher PMN percentage, and NT-proBNP, total bilirubin, CRP, aspartate aminotransferase, and alanine aminotransferase levels were considered predictive factors for patients with KD resistance to IVIG treatment.[13-16]

In our study a statistically significant decrease in the sodium level was observed in IVIG-resistant patients. The cause of hyponatremia is still unknown in patients with KD. Lim et al.[17] found that there was a strong negative correlation between the level of serum sodium and inflammatory factors, including CRP and interleukin-6 (IL-6) in children with KD. The most probable pathophysiologic mechanism

underlying hyponatremia is non-osmotic secretion of antidiuretic hormone (ADH). Several studies have confirmed that the release of ADH is promoted by IL-6 and tumor necrosis factor-α (TNF-α) during inflammation.[18] IL-6, TNF-α, and other cytokines participate in inflammation among KD patients in the acute phase,[19] suggesting that hyponatremia may be associated with inappropriate release of ADH. The marked increase in plasma IL-6 and TNF-α in IVIG-resistant infants compared with IVIG-responsive patients[20,21] may explain the significant hyponatremia in IVIG non-responders. In our study it was observed that hyponatremia and hypoalbuminemia were correlated with an increase in acute phase reactants in IVIG-resistant patients. In addition to KD, studies involving patients with inflammatory diseases, such as pneumonia, urinary tract infections, and lupus erythematosus, also demonstrated that hyponatremia is an important marker for severity and prognosis.[22,23] The mechanisms underlying hypoalbuminemia consist of the following: increased vascular permeability leading to leakage of albumin,[24,25] liver dysfunction resulting in decreased albumin synthesis; and a lack of essential amino acids due to low nutrient intake or malnutrition, resulting in reduced albumin synthesis.[26]

In our study thyrombocytosis was detected in patients with CAL and IVIG resistance. This increase was statistically significant in CAL patients. Although some studies recognized both thrombocytopenia and significant thrombocytosis as predictors of CAA or IVIG resistance; however, the majority of studies showed no association.[27,28] The mechanism underlying thrombocytosis is unclear. It has been suggested that the elevated thrombopoietin level caused by acute inflammatory responses can lead to thrombocytopoiesis.[29]

In our study IVIG resistance was detected in 12.4% of the patients. When the group developing coronary artery aneurysms was examined, we found that aneurysms developed more frequently in < 1 year and the risk of developing IVIG resistance and length of hospital stay were significantly increased. Several studies have reported that the frequency of developing CAA increases in < 1 year and > 5 years.[5,6] Based on a meta-analysis, when patients who were IVIG-resistant and -responsive were compared, the hemoglobin level, leukocyte and platelet counts, and ESR were statistically significant.[30] In our study the increased risk of IVIG resistance was shown to be statistically significant, especially in the group < 5 years of age. When the laboratory findings of our IVIG-resistant patients were examined, a significant increase existed in the leukocyte count (marked neutrophil increase), platelet count, and CRP, ALT, troponin T and NT-proBNP levels, while the hematocrit and sodium levels were significantly decreased.

Although IVIG is the established treatment for acute KD,[2,3] in some studies < 10% of patients with KD were resistant to this treatment. Patients resistant to IVIG were at a higher risk of developing CALs than patients responding to IVIG.[15,16]

Considering the frequency of IVIG resistance by age group, a significant increase in risk occurred in infants ($p < 0.001$). In our study the risk of developing IVIG resistance increased as age decreased. Indeed, there are several studies with similar results.[30-33]

Conclusion

As a result, KD patients in Turkey, in terms of development-related coronary complications, have a higher risk. It is important to identify factors that increase the risk of coronary complications and IVIG resistance in KD. Because the risk of CAA is always higher in IVIG-resistant patients, predicting IVIG resistance may play a role in reducing the development of CAA.

Abbreviations

AHA: American Heart Association

CAA: coronary artery aneurysm

CALs: coronary artery lesions

CRP: C-reactive protein

ESR: erythrocyte sedimentation rate

IVIG: intravenous immunoglobulin

KD: Kawasaki disease

LAD: left anterior descending artery

LCA: left coronary artery

LCx: left circumflex artery

LMCA: left main coronary artery

RCA: right coronary artery

Declarations

Ethics approval and consent to participate

The study protocol was approved by the University of Health Science, Kanuni Sultan Suleyman Research and Training Hospital Human Investigation Committee (HIC) (protocol number 48865165-302.14.01).

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Both authors declare that they have no competing interests.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Authors' contributions

KO: carried out the management of the research and the cardiological evaluation of the patients, encouraged Dr. Varli, reviewed and revised the article, supervised the project. YZV: Researched the literature, performed statistical analysis of the data of the cases and contributed to the writing of the article. All authors were contributors to the writing of the manuscript and formation of tables. All authors read and approved the final manuscript.

Acknowledgements

The authors acknowledge the contributions of Assoc. Prof. Nuray Aktay Ayaz from the Department of Pediatric Rheumatology.

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Tables

Table 1.Frequency diagnostic criteria met in patients

Clinical Findings	Total (n:259) (%)	Typical KD (n:80) (%)	Incomplete KD (n:179) (%)
Changes of the lips and oral mucosa	**206 (79.5%)**	75 (93.8%)	131 (73.2%)
Conjunctival congestion	**168 (64.9%)**	70 (87.5%)	98 (54.7%)
Cervical lymphadenopathy	**124 (47.9%)**	57 (71.3%)	67 (37.4%)
Rash	**179 (69.1%)**	72 (90%)	107 (59.8%)
Peripheral-extremity changes	**140 (54.1%)**	58 (72.5%)	82 (45.8%)

KD: Kawasaki Disease

Table 2. Demographic data of patients in the development of coronary artery aneurysm

Variable	Development of coronary aneurysm		*P* value
	Normal (n = 229)	CAA (n = 30)	
Gender			0.194[a]
Male	140 (61.1%)	22 (73.3%)	
Female	89 (38.9%)	8 (26.7%)	
Age range	2.94 (0.11–9.9)[d]	0.71 (0.19–9.78)[d]	**<0.001[b]**
Total fever days	6 (1–20)[d]	6 (2–15)[d]	0.896[b]
Age group			**<0.001[c]**
<1 year	32 (14%)	16 (53.3%)	
1≤ and <5 years old	141 (61.6%)	9 (30%)	
≥5 years old	56 (24.5%)	5 (16.7%)	
Hospitalization time (days)	10 (3–35)[d]	13 (6–35)[d]	**0.003[b]**
IVIG resistance frequency	16 (75%)	16 (35.6%)	**<0.001[a]**
Type of diagnosis			0.341[a]
Typical KD	73 (91.3%)	7 (8.8%)	
Incomplete KD	156 (87.2%)	23 (12.8%)	

[a] Pearson chi-square test was used

[b] Mann-Whitney U test was used

[c] significant difference was observed in the < 1 year of age group

[d] "Median" and "lowest - highest values" in parentheses were specified for non-normally distributed data

CAA: Coronary artery aneurysm; IVIG: intravenous immunoglobulin

Table 3. Demographic data of patients in response to IVIG treatment

Variable	IVIG responsiveness		*P* value
	Responders (n = 227)	Non-responders (n = 32)	
Gender			0.701[a]
Male	141 (62.1%)	21 (65.6%)	
Female	86 (37.9%)	11 (34.4%)	
Age range	3.06 (0.16–9.9)[d]	1.12 (0.11–9.78)[d]	**0.002[b]**
Total fever days	5 (1–20)[d]	6 (1–20)[d]	**0.028[b]**
Age group			**<0.001[c]**
<1 year of age	33 (14.5%)	15 (46.9%)	
1≤ and <5 years of age	136 (59.9%)	14 (43.8%)	
≥5 years of age	58 (25.6%)	3 (9.4%)	
Hospitalization time (days)	10 (3–35)[d]	14 (5–35)[d]	**0.005[b]**
Coronary involvement	29 (12.8%)	16 (50%)	**<0.001[a]**
Type of diagnosis			0.718[a]
Typical KD	71 (88.8%)	9 (11.3%)	
Incomplete KD	156 (87.2%)	23 (12.8%)	

[a] Pearson chi-square test was used

[b] Mann-Whitney U test was used

[c] significant difference was observed in the < 1 year age group

[d] "Median" and "lowest - highest values" in parentheses were specified for non-normally distributed data

IVIG: intravenous immunoglobulin

Table 4. Central tendency and variability measures of laboratory data according to coronary involvement

Variable	Normal	Coronary involvement	*P* value
	(n = 214)	(n = 45)	
Sedimentation	67.35 (27.47)[c]	66.64 (28.86)	0.880[a]
WBC	13 000 (1 000– 49 570)[d]	14 950 (5 290– 36 800)[d]	**0.002[b]**
NEU (%)	61.74 (16.88)[c]	59.70 (19.12)[c]	0.504[a]
Hematocrit	32.19 (4.14)[c]	30.65 (4.47)[c]	**0.032[a]**
PLT	374 000 (51 000–2 099 000)[d]	482 000 (162 000–1 395 000)[d]	**0.001[b]**
C-reactive protein	67.9 (1–417.4)[d]	93.5 (3.1–369)[d]	**0.044[b]**
Total protein	7.1 (1.16)[c]	6.53 (0.8)[c]	**0.001[a]**
Albumin	3.68 (0.51)[c]	3.49 (0.46)[c]	**0.037[a]**
AST	34 (4–628)[d]	38 (15.3–1 230)[d]	0.642[b]
ALT	24 (4–705)[d]	26 (8–704)[d]	0.307[b]
Na	135.03 (3.25)[c]	135.33 (3.23)[c]	0.591[a]
K	4.46 (0.59)[c]	4.76 (0.75)[c]	**0.020[a]**
Urea	18 (1–95)[d]	14 (1–57)[d]	**0.003[b]**
Creatinine	0.3 (0.09–1.03)[d]	0.27 (0.13–0.8)[d]	**0.006[b]**
Troponin T	0.003 (0.003–0.03)[d]	0.007 (0.003–0.127)[d]	**0.034[b]**
NT-proBNP	241 (55–35 000)[d]	1 248 (196–35 000)[d]	**0.016[b]**

[a] Independent sample t-test was used for parametric testing

[b] Mann-Whitney U test was used for non-parametric testing

[c] "Average" and "standard deviation" values in parentheses were specified for normally distributed data

[d] "Median" and "lowest - highest values" in parentheses were specified for non-normally distributed data

ALT: alanine transaminase; AST: aspartate aminotransferase; K: potassium; Na: sodium; NEU (%): neutrophil/leukocyte ratio; PLT: platelet count; NT-proBNP: N-terminal-pro-brain natriuretic peptide; WBC: White blood cell

Table 5. Central tendency and variability measures of laboratory data according to IVIG resistance

Variable	Responders (n = 227)	Non-responders (n = 32)	*P* value
Sedimentation	66.9 (27.18)[c]	69.44 (30.97)	0.629[a]
WBC	13 000 (1 000–49 570)[d]	18 000 (6 320–33 230)[d]	**<0.001[b]**
NEU (%)	60.62 (17.27)[c]	65.07 (17.55)[c]	0.190[a]
Hematocrit	32.15 (4.23)[c]	30.38 (4.07)[c]	**0.029[a]**
PLT	399 000 (51 000–2 099 000)[d]	409 500 (195 000–1 356 000)[d]	0.621[b]
C-reactive protein	67 (1–417.4)[d]	107.2 (4.8–369)[d]	**0.015[b]**
Total protein	7.03 (1.16)[c]	6.63 (0.89)[c]	0.183[a]
Albumin	3.65 (0.51)[c]	3.53 (0.45)[c]	0.298[a]
AST	34 (11–604)[d]	38.5 (4–1 230)[d]	0.245[b]
ALT	24 (4–527)[d]	35 (5–705)[d]	**0.033[b]**
Na	135.35 (3.18)[c]	133.83 (3.29)[c]	**0.010[a]**
K	4.48 (0.61)[c]	4.72 (0.73)[c]	0.051[a]
Urea	18 (1–95)[d]	16.5 (5–57)[d]	0.895[b]
Creatinine	0.3 (0.09–1.03)[d]	0.25 (0.16–0.8)[d]	**0.030[b]**
Troponin T	0.005 (0.003–0.17)[d]	0.068 (0.008–0.127)[d]	**0.026[b]**
NT-proBNP	329 (55–35 000)[d]	19 792 (4584–35 000)[d]	**0.014[b]**

[a] Independent sample t-test was used for parametric testing

[b] Mann-Whitney U test was used for non-parametric testing

[c] "Average" and "standard deviation" values in parentheses were specified for normally distributed data

[d] "Median" and "lowest - highest values" in parentheses were specified for non-normally distributed data

ALT: alanine transaminase; AST: aspartate aminotransferase; K: potassium; Na: sodium; NEU (%): neutrophil/leukocyte ratio; PLT: platelet count; NT-proBNP: N-terminal-pro-brain natriuretic peptide; WBC: White blood cell