Elevated Serum Free Carnitine Levels in Children with Kawasaki Disease and Their Relation to Unresponsiveness to Intravenous Immunoglobulin: retrospective study

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Abstract

Background: Carnitine plays an essential role in transfer of long-chain fatty acids to mitochondria for subsequent β-oxidation. No studies to date have characterized carnitine in children with KD. The objective of this study is to investigate the characteristics of serum free carnitine (FC) in hospitalized pediatric patients with Kawasaki disease (KD).

Methods: In total, 45 patients with KD measured the levels of serum FC from October 2018 to December 2019 were analyzed retrospectively. We analyzed the clinical and laboratory parameters just before the Intravenous immunoglobulin (IVIG) including serum levels of serum FC with respect to the IVIG response. We also analyzed the relationship between serum FC and liver deviation enzymes or the duration of fever at diagnosis.

Results: The median age was 33 months. IVIG was effective in 33 children (responders) and was ineffective in 12 (non-responders). The serum FC levels were higher in non-responders than in responders [(35.3 mmol/L (range, 26.8-118.4 mmol/L) vs. 31.4 mmol/L (range, 20.9-81.2 mmol/L), p value = 0.0496]. The FC levels before intravenous immunoglobulin (IVIG) in four-fifths of responders were below the normal range. The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and FC were higher in non-responders than in responders. There were no different in patient characteristics and laboratory data according to fever duration at diagnosis. There was a correlation between FC and AST ($R2=0.364$, $P=0.0015$) and between FC and ALT ($R2=0.423$, $P<0.001$) levels.

Conclusion: FC levels were upregulated in patients with KD who were refractory to IVIG. Additionally, FC levels in children with KD correlated with AST and ALT levels. The pathogenesis resulting in the elevation of FC levels remains elusive. Further studies are necessary to understand more precisely carnitine properties in patients with KD.

Background

Kawasaki disease (KD) is an acute systemic vasculitis that occurs mainly in infants. Coronary artery lesions (CAL) are a serious complication of KD, and thus, its prevention is important to improve outcome in children with KD. Intravenous immunoglobulin (IVIG) has been known to be effective in abolishing vascular inflammations that could lead to CAL. In patients at high risks of unresponsiveness to IVIG, steroid combination therapy with IVIG is used to avoid CAL. In previous studies, several factors have been suggested as a biomarker that could predict unresponsiveness to IVIG, such as neutrophil counts, C-reactive protein (CRP) and procalcitonin levels [1, 2, 3, 4, 5, 6]. In Japan, Gunma, Kurume, and Osaka scores are commonly used to predict unresponsiveness to IVIG [7, 8, 9]. In these scoring systems, platelet (PLT) counts, serum sodium (Na), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), and CRP are included as parameters.

Carnitine (β-hydroxy-γ-trimethylammonium butyrate) is a hydrophilic quaternary amine that plays an essential role in energy metabolism. The main function of carnitine is the transfer of long-chain fatty

acids to mitochondria for subsequent β-oxidation [10]. Carnitine homeostasis reflects the balance among absorption from the diet, endogenous biosynthesis, and efficient renal reabsorption [11]. Our preliminary study showed that several patients with KD had high levels of serum free carnitine (FC) [12] and some of these patients were unresponsive to IVIG.

No studies to date have characterized carnitine in children with KD. Here, we conducted a retrospective analysis of serum FC levels to understand properties of carnitine in children with KD.

Methods

In this retrospective study, we collected children with KD who were hospitalized in the Department of Pediatrics of Aichi Medical University Hospital from October 2018 to December 2019. This study was approved by the ethics committee of Aichi Medical University Hospital (Approval No. 2015-H830). The diagnosis of KD was performed based on the Japanese diagnostic guidelines for KD [13]. A complete KD (cKD) was diagnosed when a child had five or more of the six major symptoms, while an incomplete KD (iKD) was diagnosed when a child had four or fewer major symptoms after exclusion of other illnesses with similar clinical features, such as viral and bacterial infections, cervical lymphadenitis, and toxic shock syndrome. In our hospital, children with KD were treated with IVIG and oral administration of aspirin at a dose of 30–50 mg/kg/day immediately after the diagnosis. If patients had liver dysfunction, aspirin was substituted by 3–5 mg/kg dose of oral flurbiprofen. Steroids were used for patients expected to be unresponsive to IVIG based on prediction scores, such as Gunma [7], Kurume [8], and Osaka scores [9]. Steroids were usually administered if two or more of the above scores indicated unresponsiveness to IVIG and based on the recommendation of the attending pediatricians. In this study, responders to IVIG were defined as those children who did not have pyrexia after IVIG administration. Non-responders to IVIG were defined as those children who had persisting or recurrent pyrexia for more than 24 hours after IVIG, thereby necessitating a second line of treatment. In this study, patients who needed steroid combination therapy were included as non-responders.

We recruited the following laboratory data before IVIG: white blood cell (WBC) count, neutrophil count, hemoglobin (Hb), PLT count, T-Bil, albumin, AST, ALT, Na, CRP, D-dimer, brain natriuretic peptide, and FC levels. Some of these factors were previously reported to be useful in predicting unresponsiveness to IVIG [1-9] and can be always measured in most hospitals. According to the 2018 Japanese guide for the diagnosis and treatment of carnitine deficiency [14], low, normal, and high FC were defined as serum FC level < 36 μmol/L , 36 μmol/L £ FC £ 74 μmol/L, and FC > 74 μmol/L, respectively. Additional information collected from medical records includes age, gender, history of taking pivalate-conjugated antibiotics within 2 weeks before hospitalization, dates of illness prior to administration of IVIG, duration of hospitalization, ratios of cKD and iKD, and CAL after discharge.

We compared demographic and laboratory data according to the serum FC levels (low, normal, and high). We also explored the relation between serum FC levels, and sampling days of illness (< 4 days, 5-6 days, and > 7 days) and the presence or absence of AST/ALT elevation. AST/ALT elevation was defined as AST

>39 IU/L and/or ALT >45 IU/L. The chi-square test and Kruskal-Wallis test were applied to compare categorical and numerical variables among three groups, respectively. For multiple comparison of numerical variables among 3 groups, the Steel-Dwass test was used when Kruskul-Wallis test showed a p value <0.05. We performed residual adjustment analysis, when the chi-square test yielded a p value <0.05. An absolute adjustment residual >2 was considered to be statistically significant. In addition, demographic and laboratory data including serum FC levels were compared between IVIG responders or IVIG-non-responders in order to clarify the predictive values for IVIG unresponsiveness. The Fisher's exact and Mann–Whitney U tests were used to compare categorical and numerical variables, respectively. The association between FC levels and other laboratory data was analyzed with Pearson's correlation test. In addition, serial changes in FC levels in responders and non-responders were compared using the Kruskal-Wallis test followed by the Steel-Dwass test. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with the XLSTAT ver. 2019.1.3 software (Addinsoft; Okayama, Japan).

Results

In total, 76 children with KD were hospitalized during the study period. We excluded 29 children in whom FC levels were not measured and 2 children who did not undergo IVIG. Following these exclusions, 45 patients were further analyzed in this study. The median age was 33 months, while 20 and 25 patients were male and female, respectively. The median day of illness at the initiation of IVIG was 5 (range, 3–12 days). Ten patients were diagnosed as iKD, while CAL was not observed in any patient during this study period. IVIG was effective in 33 patients (responders) and ineffective in 12 patients (non-responders).

Table 1 shows demographic and laboratory data of the patients according to serum FC levels. Low FC was observed in 33 patients, normal FC was observed in 7 patients, and high FC was observed in 5 patients. There were no significant differences in the demographic data except for gender. Regarding the sampling days of illness, serum FC levels were not different according to the sampling days of illness. Demographic or laboratory data were not different according to the sampling days of illness (Supplementary table 1). Among the laboratory data, T-Bil was higher in high FC group than low and normal FC groups, and AST, ALT, and D-dimer levels were higher in high FC group than in normal FC group. All patients with high serum FC levels had elevated AST/ALT, although the difference among the groups was marginal. Serum FC levels were higher in patients with elevated AST/ALT than in patients with normal AST/ALT (Supplementary table 2). T-Bil was also higher in patients with elevated AST/ALT than in patients with normal AST/ALT. The correlation between serum FC levels and laboratory data is shown in Figure 1. There was a significant correlation between FC, and AST (R^2 = 0.364, P = 0.0015) and ALT (R^2 = 0.423, P < 0.001). However, no significant correlation was observed between FC and T-Bil.

Table 2 shows demographic and laboratory data between IVIG responders and non-responders. There was no difference in demographic data between responders and non-responders except for the duration of hospitalization. FC levels as well as T-Bil, AST, and ALT were higher in non-responders than in responders. The median serum FC level was 31.4 mmol/L (range, 20.9-81.2 mmol/L) and 35.3 mmol/L

(range, 26.8-118.4 mmol/L) in responders and non-responders, respectively (p = 0.0496). The serial changes in FC levels is shown in Figure 2. In responders, serum FC levels at discharge were higher than before and after IVIG. On the other hand, no statistical differences in FC levels were observed according to the timing of sampling in non-responders, although FC levels were decreased after IVIG and then were mildly elevated at discharge.

We also analyzed the predictive value of FC levels that could correspond to unresponsiveness to IVIG. The area under the receiver-operating characteristic curve (ROC) or AUC of the FC level was 0.69 (95% confidence interval, 0.51–0.87) (Figure 3). After applying the cut-off value (34.7 mmol/L) to the FC level, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.667, 0.758, 0.500, and 0.862, respectively.

Discussion

Our study revealed unique characteristics of carnitine in patients with KD. An elevation of FC levels was observed in some patients with KD before IVIG, whereas FC levels were low in the majority of patients with KD. Additionally, FC levels before IVIG were higher in non-responders than in responders. The high FC level correlated with unresponsiveness to IVIG; however, its predictive value was considered to be insufficient. Moreover, FC levels correlated with AST and ALT levels.

Our preliminary study showed that low serum FC levels were very common in hospitalized children with febrile illness [12]. An elevated level of FC represents an exceptional pathological state, such as acute renal failure [17] and liver cirrhosis [18]. In contrast, various congenital and acquired conditions are known to cause carnitine deficiency [19]. Thus, it is remarkable that high FC was seen in some children with KD. Currently, the pathogenesis resulting in the elevation of FC levels in children with KD remains elusive. Carnitine is primarily stored in skeletal muscle, liver, myocardium, and brain. As such, injuries to these organs could lead to carnitine leakage into the bloodstream. We hypothesize that liver injury is likely to result in an elevation of FC levels in children with KD, because FC levels in our study closely correlated with AST and ALT levels, which are well known markers associated with liver injury. High FC levels were exclusively observed in patients with elevated AST/ALT. This hypothesis should be evaluated by further clinical and experimental studies.

It is interesting that FC levels in children with KD were related to IVIG unresponsiveness, although its predictive value may be insufficient. In this study, not only FC levels but also T-Bil, AST, and ALT level were associated with unresponsiveness to IVIG. Previous studies have shown that these values were higher in non-responders than in responders [20, 21, 22]. It is remarkable that all these factors have also been incorporated into the existing refractory prediction scores, such as Osaka, Kurume, and Gumma scores [7, 8, 9]. As mentioned above, FC levels closely correlated with AST and ALT levels. Thus, the correlation between FC and IVIG unresponsiveness indicates that an elevation of FC levels in children with KD could be a reflection of pathogenesis that could lead to IVIG unresponsiveness. IVIG unresponsiveness in children with KD has been presumed to correlate with the severity of inflammation [23, 24].

Proinflammatory cytokines such as interleukin (IL)-1 and IL-6 have been known to be related to IVIG unresponsiveness. Fury et al. reported transcript abundance of IL-1 pathway genes and MMP-8 in patients with IVIG resistant KD patients [25]. This suggests that IL-1 pathway activation could be related to IVIG unresponsiveness. IL-6 is also associated with various biological functions, such as an increase in acute-phase proteins, T cell activation, procoagulant effects and thrombocytosis, which could lead to resulting in IVIG unresponsiveness [26, 27, 28]. An elevation of FC levels as well as AST, ALT, and T-Bil levels could be attributable to tissue damage that resulted from inflammation induced by proinflammatory cytokines. Regarding the predictive value of FC levels, the sensitivity and specificity were 0.794 and 0.583, respectively, and the AUC was 0.69. While FC levels alone were not accurate enough to predict unresponsiveness to IVIG, these levels in combination with other variables such as AST, ALT, and T-Bil, could become as useful as the Gunma, Kurume, and Osaka scores.

It is noteworthy that FC levels were below the normal range in the majority of responders in this study. This could be attributable to an increased carnitine requirement caused by systemic inflammation in children with KD. It is well known that secondary carnitine deficiency could result from decreased body storage and increased requirements in patients with sepsis [29, 30]. This suggests that patients with systemic inflammation, including KD, will be at a risk of secondary carnitine deficiency. In this study, the magnitude of lower FC levels was not severe in children with KD. There were no patients with carnitine deficiency (FC levels below 20 μmol/L), or symptoms related to low FC levels such as hypoglycemia. We consider that carnitine supplementation is unnecessary in patients with KD.

Serum FC levels were not different according to sampling days of illness, which is presumed to reflect the intensity of systemic inflammation. It is reported that, in the acute febrile stage of KD, the intensity of systemic inflammation may gradually increase and reach the peak (mean at 6th febrile day) [15]. AST and ALT are mainly elevated before peak of the inflammation [16]. The results of our study suggests that serum FC levels may not be directly associated with systemic inflammation. Carnitine deficiency can be observed in patients with sepsis, which causes serious systemic inflammation.

This study has some limitations. First, this is a single center retrospective study with a small number of patients. Therefore, the results of this study should further be verified in other cohorts of patients. Second, serum FC levels were not measured in all children with KD during the study period. As such, prospective studies are necessary to identify carnitine properties in patients with KD more accurately. Finally, we did not examine other clinical data such as triglyceride and ammonia, which could be affected by FC levels. Thus, further studies on these clinical variables are necessary to elucidate the impact of FC levels in children with KD.

Conclusions

In conclusion, FC levels were higher in some children with KD. While FC levels were higher in non-responders than in responders, the correlation between FC levels and IVIG unresponsiveness was not significant. Additionally, FC levels in children with KD correlated with AST and ALT levels. Currently, the

pathogenesis resulting in the elevation of FC levels in children with KD remains elusive. Further studies are necessary to understand more precisely carnitine properties in patients with KD.

List Of Abbreviations

Kawasaki disease (KD)

Coronary artery lesions (CAL)

Intravenous immunoglobulin (IVIG)

C-reactive protein (CRP)

platelet (PLT)

sodium (Na)

aspartate aminotransferase (AST)

alanine aminotransferase (ALT)

total bilirubin (T-Bil)

free carnitine (FC)

white blood cell (WBC)

hemoglobin (Hb)

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Aichi Medical University Hospital (Approval No. 2015-H830). Waiver of informed consent was also approved, because we retrospectively analyzed the existing data with no identifiable private information and notification with opt-out was shown in the hospital.

Declarations

Not applicable

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from

the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

TM and AO conceived of the study, collected data, performed the analysis, and drafted the manuscript. TM, NN, YM, SN, SK, TH, RM, KM, HM, YK, MA, HI, HK YS, TN, TH, HA and AO collected data and assisted in interpretation of data. All the authors of the study gave final approval for the published manuscript and agree to be accountable for all aspects of this work.

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Tables

Table 1. Demographic and laboratory data before IVIG according to serum free carnitine level

	Free carnitine levels			
	Low (< 36 mmol/L)	Normal (36 £ £ 74 mmol/L)	High (> 74 mmol/L)	P value
	N=33	N=7	N=5	
Age (months)	37 (8-84)	31 (8-67)	9 (6-50)	0.396
Gender (M:F)	11:22	5:2	4:1	0.0434
PCA within 2 weeks	7 (21.2%)	0 (0.0%)	1 (20.0%)	0.407
Incomplete KD	7 (21.2%)	1 (14.3%)	2 (40.0%)	0.552
Days of illness at IVIG (days)	5 (3-10)	5 (4-12)	4 (4-5)	0.387
Responders to IVIG	26 (78.8%)	5 (71.4%)	2 (40.0%)	0.187
Duration of hospitalization (days)	8 (5-15)	8 (7-11)	10 (8-13)	0.0820
Sampling days of illness				
< 4 days	15	2		
5-6 days	13	3	3	0.692
≥ 7 days	5	2		
			2	
			0	
WBC (/mL)	13000 (7100 - 26500)	12900 (6000 - 20000)	15800 (11900 - 25000)	0.366
Neutrophil (%)	74 (40 - 95)	77 (46 - 84)	70 (63 - 96)	0.919
Hb (mg/dL)	11 (8.4 - 14)	11 (10.4 - 12.1)	10.5 (9 - 11.4)	0.396
Platelet count (/mL)	350000 (170000 - 784000)	315000 (209000 - 463000)	316000 (235000 - 499000)	0.969
T-Bil (mg/dL)	0.53 (0.29 - 1.01)	0.53 (0.17 - 0.99)	2.235 (1.55 - 2.53)	0.0047§
Albumin (g/dL)	3.3 (2.2 - 4)	3.4 (2.9 - 3.6)	3.2 (2.7 - 3.5)	0.598
AST (IU/L)	35 (16 - 288)	64 (22 - 309)	378 (70 - 2729)	0.0045†
ALT (IU/L)	25 (5 - 331)	30 (9 - 413)	191 (43 - 861)	0.0164‡
Elevated AST/ALT				0.053
Yes	14 (42.4%)	4 (57.1%)	5 (100%)	
No	19 (57.6%)	3 (42.9%)	0 (0%)	
Na (mEq/L)	135 (129 - 141)	136 (130 - 138)	134 (132 - 137)	0.470
D-dimer (ng/mL)	1.53 (0.89 - 13.33)	1.42 (1.1 - 2.45)	2.875 (2.09 - 4.24)	0.0218¶
BNP (pg/mL)	40.6 (2 - 810.5)	22.7 (3.1 - 106.1)	167.2 (71.1 - 464.8)	0.0551
CRP (mg/dL)	8.27 (1.85 - 16.47)	5.88 (2.55 - 14.92)	7.34 (6.62 - 13.49)	0.483

PCA: pivalate-conjugated antibiotics, KD: Kawasaki disease, IVIG: intravenous immunoglobulin, WBC: white blood cell counts, Hb: hemoglobin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BNP: brain natriuretic peptide, CRP: C-reactive protein, FC: free carnitine, NS: not significant

Elevated AST/ALT was defined as AST>39 and/or ALT>45

- Low vs High: p=0.0031, Normal vs High: p=0.0198

† Low vs High: p= 0.0038

‡ Low vs High: p=0.0117

¶ Low vs High: p= 0.0174

Table 2. Demographic and laboratory data before IVIG between responders and non-responders.

	Responders (N = 33)	Non-responders (N = 12)	P value
Age (months)	31 (6-84)	25 (9-54)	0.893
Gender (M:F)	15:18	5:7	> 0.99
PCA within 2 weeks	6 (18.8%)	2 (16.7%)	0.448
Incomplete KD	8 (24.2%)	2 (16.7%)	0.705
Days of illness at IVIG	5 (3-12)	4 (4-10)	0.322
Duration of hospitalization (days)	8 (5-10)	10 (7-15)	< 0.001
Coronary artery lesion	0	0	> 0.99
WBC (/mL)	13,900 (6,000-26,500)	12,550 (8,700-25,000)	0.369
Neutrophil (%)	71 (40-95)	76.5 (54-96)	0.426
Hb (mg/dL)	10.7 (8.9-14)	10.95 (8.4-12.4)	0.653
Platelet count (/mL)	350,000 (170,000-784,000)	311,000 (209,000-559,000)	0.538
T-Bil (mg/dL)	0.52 (0.17-2.53)	0.84 (0.29-2.37)	0.0344
Albumin (g/dL)	3.3 (2.2-4.0)	3.35 (3.1-3.5)	0.518
AST (IU/L)	35 (16-309)	116 (24-2729)	0.0223
ALT (IU/L)	23 (6-413)	117 (5-861)	0.0255
Na (mEq/L)	135 (129-141)	135.5 (132-138)	0.836
D-dimer (ng/mL)	1.54 (80.89-13.33)	1.635 (0.95-4.24)	0.735
BNP (pg/mL)	34.55 (2.0-810.5)	43.35 (19.8-106.1)	0.813
CRP (mg/dL)	7.33 (1.85-16.47)	8.685 (5.58-12.96)	0.280
FC (mmol/L)	31.4 (20.9-81.2)	35.3 (26.8-118.4)	0.0496

IVIG: intravenous immunoglobulin, WBC: white blood cell counts, Hb: hemoglobin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BNP: brain natriuretic peptide, CRP: C-reactive protein, FC: free carnitine

Figures

Figure 1.

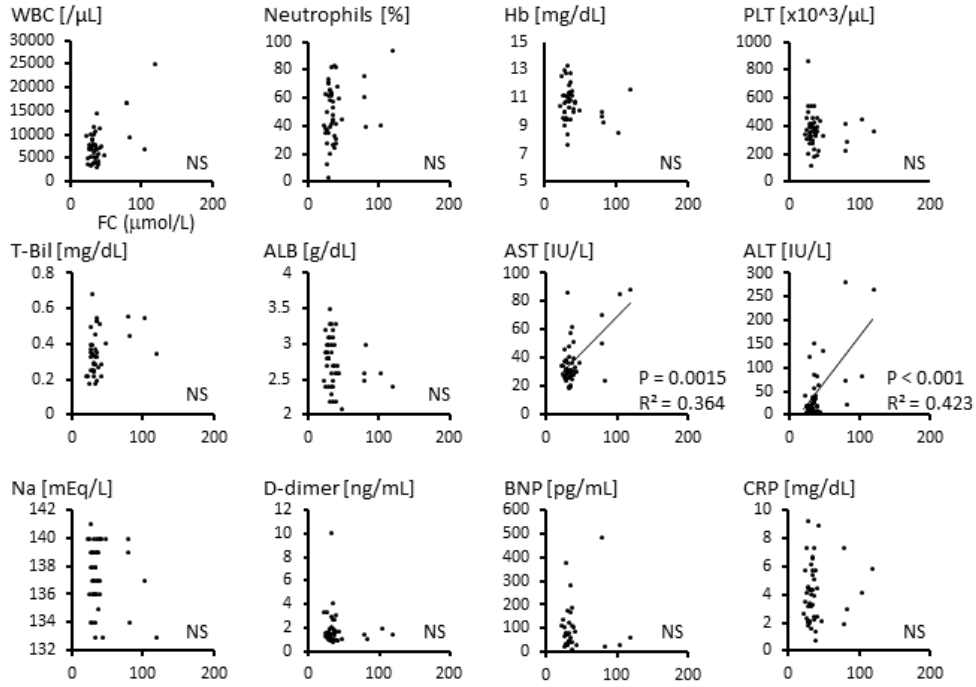

Figure 1

Correlation between serum free carnitine (FC) and other laboratory data. WBC: white blood cell, Hb: hemoglobin, PLT: platelet, T-Bil: total bilirubin, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Na: serum sodium, BNP: brain natriuretic peptide, CRP: C-reactive protein

Figure 2.

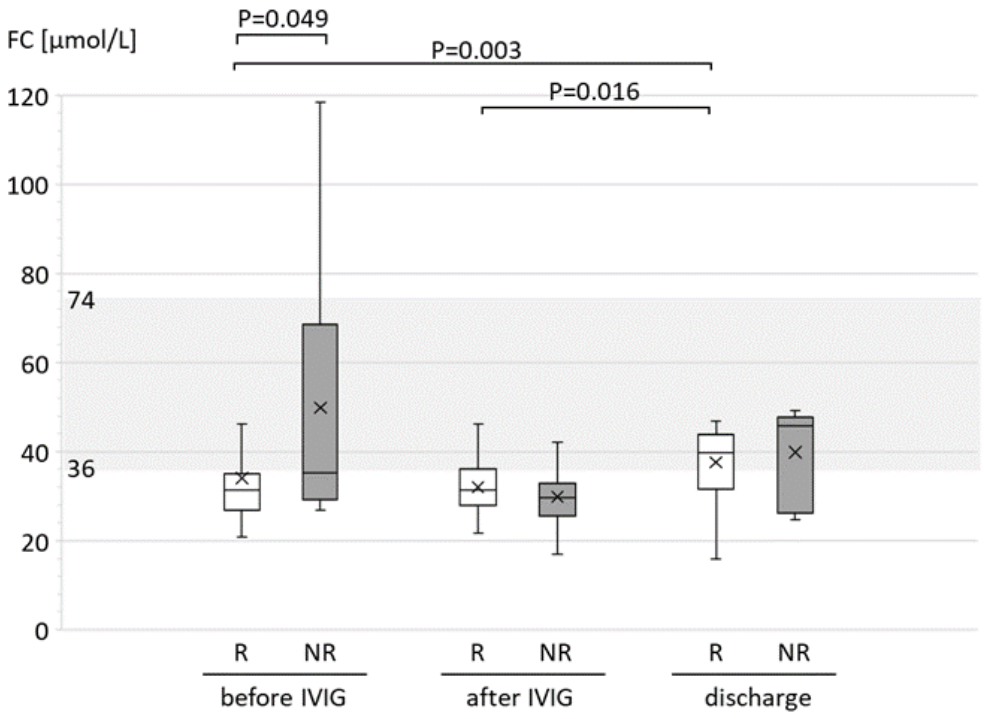

Figure 2

Serial changes in serum free carnitine of responders and non-responders. The normal range of serum free carnitine is indicated by grey band. FC: free carnitine, R: responders to IVIG, NR: non-responders to IVIG

Figure 3.

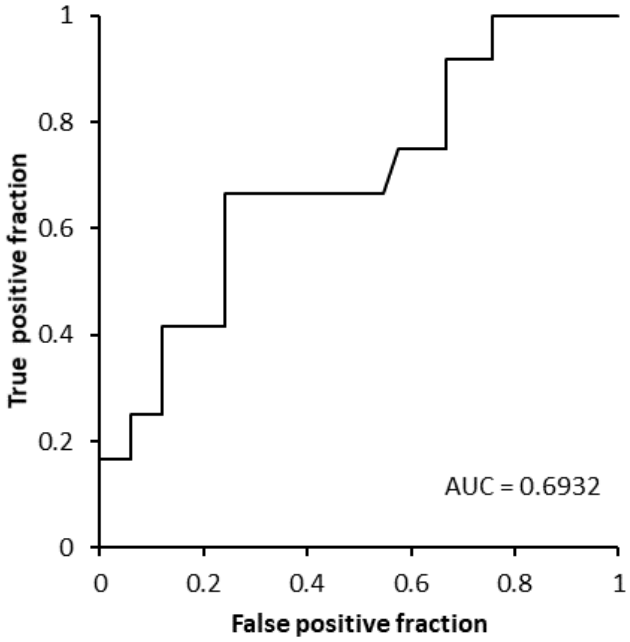

Figure 3

Receiver operating characteristic curve of free carnitine to predict unresponsiveness to intravenous immunogloburin. AUC: area under the curve

Supplementary Files

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- Suppl.table.reviced.docx