A quick and improvement effect of leucine enriched dietary supplement on malnutrition in acute stroke patients receiving enteral tube feeding

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Research article

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Abstract

Background:

Malnutrition often occurs in acute stroke patients receiving enteral tube feeding (ETF). Unless malnutrition is improved, their clinical outcome is poor. However, strategies to improve malnutrition in these patients have not been established. Branched-chain amino acids (BCAA) may enhance protein synthesis and attenuate inflammation. Our study aimed to investigate whether a leucine enriched BCAA dietary supplement (LEBDs) could quickly improve a patient's nutritional status during the early stage of malnutrition.

Methods:

We retrospectively analyzed acute stroke patients who 1) were admitted between December 2016 and July 2017; 2) underwent ETF for seven days or longer after admission; 3) who underwent blood examination on admission, the 5th day, and seventh day; 4) in whom transthyretin (TTR) was less than 15 mg/dl on the 5th day, and 5) received LEBDs containing 1.44 g leucine per 200 kcal twice a day on the 5th day. We evaluated patients' features, serum albumin (Alb) (g/dl), transthyretin (TTR) (mg/dl), and high sensitive C-reactive protein (CRP) (mg/dl) on admission, the fifth day, and the seventh day.

Results:

Fifteen patients met our inclusion criteria. Their median age, body mass index (BMI), body weight (BW), serum blood glucose (BG), Alb, TTR, and CRP were 82 years, 21.8 kg/m2, 50 kg, 150 mg/dl, 3.5 g/dl, 12.7 mg/dl, and 1.02 mg/dl, respectively. Their median calorie intake was 1,200 kcal/day. On the 5th day, their median Alb and TTR decreased to 2.6 g/dl ($p<0.0001$) and 11.8 mg/dl ($p<0.01$), respectively, and their median CRP increased to 5.24 mg/dl ($p<0.01$). On the 7th day, TTR increased to 15.7 mg/dl ($p<0.001$), and CRP decreased to 4.77 mg/dl ($p<0.05$), whereas their median Alb was 2.6 g/dl (ns) and did not significantly change.

Conclusion

The leucine enriched BCAA dietary supplement had a quick and improvement effect on the transthyretin and CRP level.

Background

Malnutrition [1–3] often occurs in severe acute stroke patients who are unable to take foods orally due to dysphagia or disturbed level of consciousness and who must receive enteral tube feeding (ETF). Malnutrition leads to the severity of the general condition and subsequently extended stay in hospital or in-hospital mortality [4–7]. Malnutrition probably causes a weakened immune system and causes infection to occur [8]. Acute inflammation associated with infection exacerbates hypoproteinemia, and the clinical outcomes in patients with severe hypoproteinemia are generally poor. If malnutrition occurs in

a patient, it should be treated and improved as soon as possible. Inflammation must be attenuated as soon as possible. However, it has not been established on how to improve hypoproteinemia rapidly [9]. Larger volumes of protein intake in the diet do not always lead to rapid improvement of hypoproteinemia and cessation of inflammation, probably due to the dysfunction of protein synthesis in a severe clinical state [10] [11]. Leucine is one of the essential amino acids and one of the branched-chain amino acids (BCAA) [12], and previous studies have reported that leucine-enriched BCAA supplement may attenuate inflammation, enhance protein synthesis [13, 14, 15]and may be useful in recovering muscle mass and strength and in promoting rehabilitation [13, 16–19]. Our study aimed to investigate whether leucine enriched BCAA dietary supplement (LEBDs) could increase serum levels of albumin (Alb) or transthyretin (TTR) early in the development of severe malnutrition within a few days after stroke onset.

Methods

We retrospectively analyzed acute stroke patients who 1) were admitted between December 2016 and July 2017, 2) started ETF on the second day and continued to undergo ETF for seven days or longer after admission, 3) underwent blood examination on admission, the fifth day and the seventh day, 4) in whom serum transthyretin (TTR) level was less than 15 mg/dl on the fifth day, and 5) received LEBDs containing 1.44 g leucine per 200 kcal twice a day on the 5th day (Table 11) added to baseline enteral nutrients. We defined TTR less than 15 mg/dl as malnutrition, as TTR is a rapid turnover protein [20].

Exclusion Criteria

We excluded from our analysis patients who died due to very severe stroke within seven days after its onset, who could take foods orally on admission, who did not undergo a thorough blood examination, or in whom their TTR was 15 mg/dl or more on the 5th day.

Target calories

We calculated the target calories for patients according to the Harris-Benedict Equation (HBE) [21].

Enteral Nutrients

We started to administer enteral nutrients on the second day of admission. Enteral nutrients (EN) we used to be IMPACT (Nestle Japan Co. Ltd.), PEPTAMEN AF (Nestle Japan Co. Ltd.), MEIN (Meiji Co. Ltd., Japan) or RENALEN MP (Meiji Co. Ltd., Japan). IMPACT includes contents that consist of 22.1% of protein (arginine-enhanced), 24.9% of lipid, and 53% of carbohydrates against 250 kcalories (kcal) per 250 ml of one pack. PEPTAMEN AF includes contents that consist of 25% of protein containing whey peptide, 40% of lipid (medium-chain triglyceride, MCT 20%), and 35% of carbohydrates against 300 kcal per 200 ml of one pack. MEIN consists of 20% of protein containing whey peptide, 25% of lipid (MCT 5.25%), and 55% of carbohydrates containing palatinose against 200 kcal per 200 ml of one pack. Renalen MP consists of 14% of protein, 25.2% of lipid, and 59.6% of carbohydrates containing palatinose against 400 kcal per 250 ml of one pack. Palatinose is a disaccharide that consists of one glucose and

one fructose, and it has a low glycemic index. Enteral nutrients except for RENALEN MP were protein-rich nutrients. Leucine-enriched BCAA dietary supplement (LEBDs) (Leucine Plus, Nestle, and Ajinomoto, Japan) consists of 8g (16%) of protein containing 1.44 g of leucine and 18.5 g (only 37%) of sugar against 200 kcal per 100 ml of one pack (Table 1).

Evaluation

We evaluated patient features, TTR, Alb, and high sensitive CRP on admission, the fifth day, the 7th day because previous studies have reported serum high sensitive C-reactive protein (CRP) (mg/dl) elevation and a decrease in albumin (Alb) (g/dl) or TTR in patients with severe inflammation or severe acute conditions [22, 23, 24]. Besides, we evaluated in-hospital clinical outcome, hospitalization days, and serum Cre on admission, the fifth day, the 7th day, because deterioration of renal function was a possible adverse effect of protein-rich EN.

Statistical analysis

For a comparison of paired variables, we used a Wilcoxon signed-rank test for non-parametric data. We performed a one-sided test and considered a probability of less than 0.05 statistically significant. We used the JMP (version 15.1) program to perform the statistical analysis.

Results

During the study period, we treated 400 acute stroke patients in our institution. Among them, 87 patients underwent ETF on the second day. Among the 87 patients, 11 patients died within seven days. Among the 76 survived patients, the TTR level on the fifth day was less than 15 mg/dl in 15 patients, and the fifteen patients received LEBDs on the 5th day. Their median age (interquartile range), woman sex (%), body mass index (BMI), and body weight (BW) were 82 (77-92) years, 9 (60%), 21.8 (17.6-23.5) kg/m2, and 50 (44-57.8) kg. They were very elderly patients. Their median Glasgow Coma Scale (GCS) [25] and Japan Coma Scale (JCS) [26] on admission were 9 and 20 (Table 2), respectively, and they suffered from impaired consciousness. Their median creatinine (Cre), estimated glomerular filtration rate (eGFR), and creatinine clearance (CCr) on admission were 0.78 (mg/dl), 56.39 (mL/min/1.73m2), and 37.95 (ml/min) [27], respectively. In 12 of the 15 patients, eGFR was less than 60 (mL/min/1.73m2), and in 9 of the 15 patients, CCr was less than 50 (ml/min). More than half of the patients suffered from renal dysfunction (Table 2). Their median target calorie and real calorie intake by EN was 1,328 and 1,200 kcal/day, respectively. The calorie status was 90.4 % of the plan on the fifth day. We used protein-rich EN except for REANALEN MP in twelve of the fifteen patients (Table 1). We added the LEBDs (2.88g of leucine/400kcal/200ml/day) to baseline EN on the fifth day.

Their median TTR on admission, the fifth day, and the seventh day was 12.7, 11.8, and 15.7 mg/dl, respectively and their median differences of TTR between on admission and the fifth day, the fifth day and the seventh day were -3.6 ($p<0.001$) and 4.1 ($p<0.001$) mg/dl, respectively (Fig. 1). Their median Alb on admission, the fifth day, and the seventh day was 3.5, 2.6, and 2.6 g/dl, respectively and their median

differences of Alb between on admission and the fifth day, the fifth day and the seventh day were -0.9 ($p<0.0001$) and 0.1 (ns) g/dl, respectively (Fig. 2). Their median high sensitive CRP on admission, the fifth day, and the seventh day was 1.02, 5.243, and 4.774 mg/dl, respectively and their median differences of CRP between on admission and the fifth day, the fifth day and the seventh day were 4.0 ($p<0.01$) and -1.9 ($p<0.05$) mg/dl, respectively (Fig. 3). Their median WBC on admission, the fifth day, and the seventh day was 9.7, 9.3, and 10.7 (ns) 10^9/L, respectively and their median differences of WBC between on admission and the fifth day, the fifth day and the seventh day were 2.7 ($p<0.05$) and -0.2 (ns) 10^9/L, respectively. Their median Glu on admission, the fifth day, and the seventh day was 150, 124, and 122 mg/dl, respectively and their median differences of Glu between on admission and the fifth day, the fifth day and the seventh day were -25 (ns) and 4 (ns) mg/dl, respectively. Their median Cre on admission, the fifth day, and the seventh day was 0.77, 0.83, and 0.81 mg/dl, respectively and their median differences of Cre between on admission and the fifth day, the fifth day and the seventh day were -0.05 (ns) and -0.05 (ns) mg/dl, respectively (Table 3).

TTR and Alb decreased soon, and CRP and WBC increased soon, although we used protein-rich EN except for REANALEN MP in twelve of the fifteen patients. We added the LEBDs (400kcal/day) to baseline EN on the fifth day. The BG level was under control over seven days (Table 3). Overall renal function did not deteriorate except for two cases. In Case 2 and 4 of 75 g protein per day with PEPTAMEN AF (25% of protein), serum Cre level acutely rose on the fifth day, and calories per day by PEPTAMEN AF was reduced from 1200 to 900 kcal from the fifth day. The LEBDs was added on 900 kcal of PEPTAMEN AF in case 2 and 4, and their Cre level did not deteriorate on the seventh day (Table 2 and 3).

Thirteen (86.7%) of the fifteen patients discharged within 17 days, and they were transferred to comprehensive rehabilitation centers on the twelfth day (median). Two of the fifteen patients (Case 8 and 13) died on the eighth day and the twenty-first day, respectively, although their TTR improved from on the fifth day to the seventh day. Median hospitalization in the fifteen patients was 12 days (IQR; 8-15) (Table 2).

Discussion

Our results demonstrate that the leucine enriched BCAA dietary supplement had a quick and improvement effect on the transthyretin and CRP level in acute stroke patients receiving enteral tube feeding.

Our patients were very elderly, suffered from impaired consciousness and renal dysfunction, and malnutrition within the five days of admission. Treatment to rescue patients with such clinical severe conditions and to improve hypoproteinemia quickly has not been established, although there are many types of enteral nutrients or dietary supplements. Extended hospitalization and high in-hospital mortality were anticipated in them. Indeed, we used protein-rich EN in twelve of the fifteen patients, but their TTR and Alb level declined. Serum Cre acutely rose in two of the twelve patients administered with protein-rich EN, and protein-rich EN induced deterioration of renal function, therefore, must be considered. We administered the LEBDs, and thirteen of the fifteen patients achieved an early discharge to

comprehensive rehabilitation centers within 17 days except for two patients. Their clinical course was not usual. We supposed that the LEBDs had a quick effect on treating malnutrition in the fifteen patients. After administration of the LEBDs, the TTR level rose soon, and the CRP level decreased soon, probably because BCAAs such as leucine played critical roles in the regulation of energy homeostasis, nutrition metabolism, gut health, immunity as they acted as potential anti-inflammatory mediators [28-30], further helped attenuate inflammation and enhance protein synthesis [13, 29, 30]. The Alb and WBC level did not change soon after the administration of the LEBDs, as the Alb level usually improves slowly. The LEBDs likely provides benefits with malnutrition patients in a stroke care unit (SCU) or intensive care unit (ICU).

Study Limitations

Our study had several limitations. Our study included a small number of patients. Moreover, all patients were likely of Japanese ancestry; therefore, not representative of the general population. Our patients started to use different types of enteral nutrients, and the LEBDs contained other nutrients except for leucine. Our study investigated short-term outcomes of blood examinations, in-hospital death, and hospitalization days but did not study the long-term effect of the LEBDs. Our study was a retrospective one. Therefore, future prospective studies are required.

Conclusion

The leucine enriched BCAA dietary supplement (LEBDs) had a quick and improvement effect on the transthyretin and CRP level, and survivors (86.7%) were transferred to comprehensive rehabilitation centers on the twelfth day. The results warrant the further clinical application of the LEBDs in acute patients with malnutrition.

List Of Abbreviations

BMI: body mass index, BW: body weight, Cre: creatinine, eGFR: estimated glomerular filtration rate, CCr: creatinine clearance, BG: blood glucose, T-CHO: total cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein, Alb: albumin, TTR: transthyretin, WBC: white blood cell, ETF: enteral tube feeding, EN: enteral nutrient, IMEN: immune-mediated enteral nutrient, IEEN: immune-enhanced enteral nutrient, BCAA; branched-chain amino acid, SD: standard deviation, LEBDs: leucine-enriched BCAA dietary supplement, mRS: modified Rankin scale, SCU; stroke care unit, ICU: intensive care unit

Declarations

Ethics approval and consent to participate

All procedures performed in the study were in accordance with the ethical standards of the institution (Shonan Kamakura General Hospital) and with the 1964 Helsinki Declaration. The Tokushukai Group Ethical Committee approved access to medical records for our retrospective analysis. Informed consent

was not required because of routine medical care, the retrospective access to medical records in very elderly, disabled stroke patients treated four year ago, and the anonymization of patient identifiers.

Consent for publication:

Not applicable

Availability of data and materials:

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

Competing Interests

The authors have no conflicts of interest to disclose.

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The authors received no specific funding for this work.

Authors' contributions

Takahisa Mori, MD, had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: T. Mori.

Patient treatment and care: T. Mori, K. Yoshioka

Acquisition of data: T. Mori, K. Yoshioka.

Interpretation of data and statistical analysis: T. Mori.

Drafting the manuscript: T. Mori.

Critical revision of the manuscript for relevant intellectual content: T. Mori.

Final approval of the submitted version: T. Mori, K Yoshioka

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Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

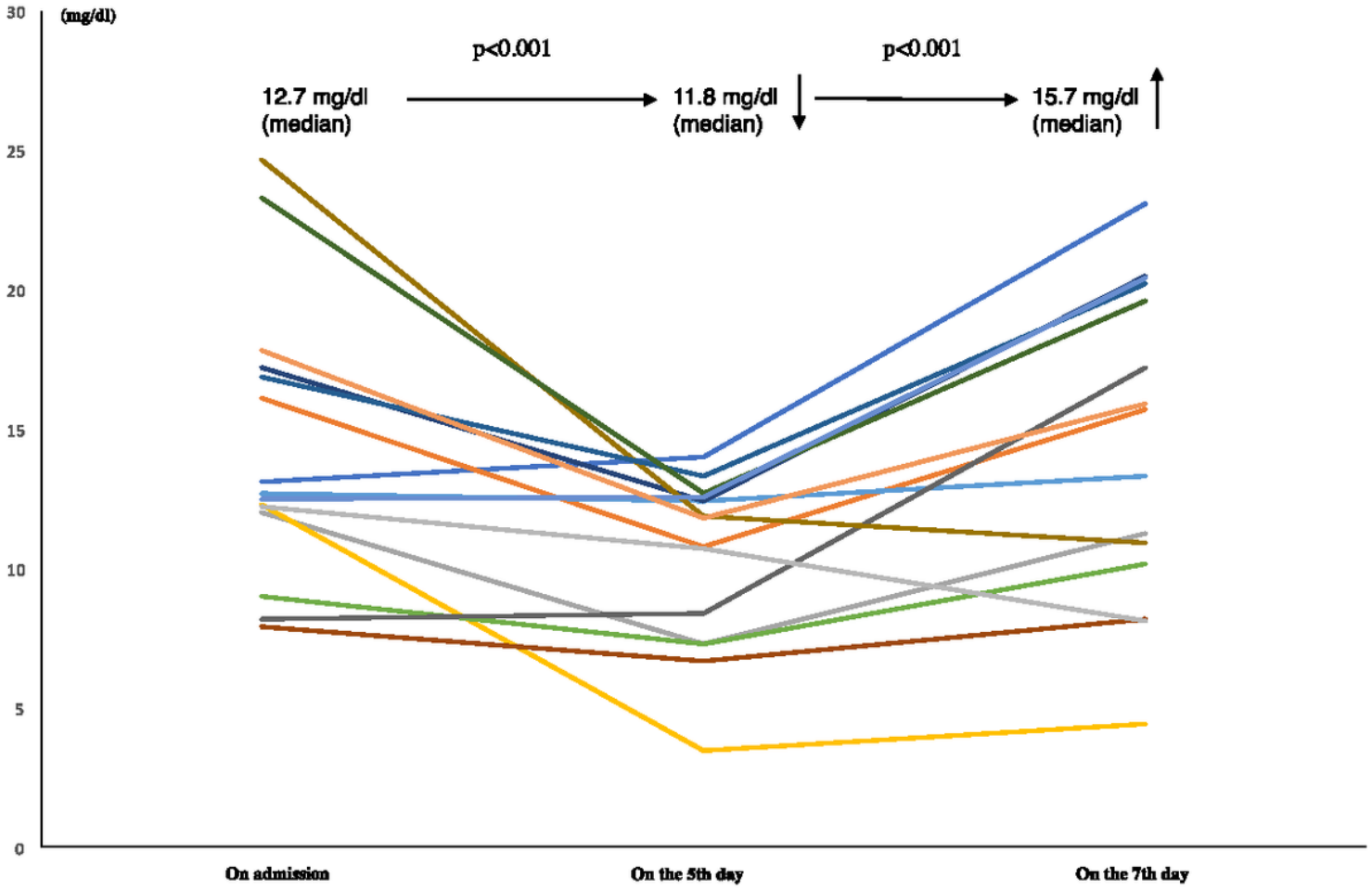

Figure 1

Serial changes of serum transthyretin (TTR) on admission, on the fifth day, and the seventh day. One-sided Wilcoxon signed-rank test was performed.

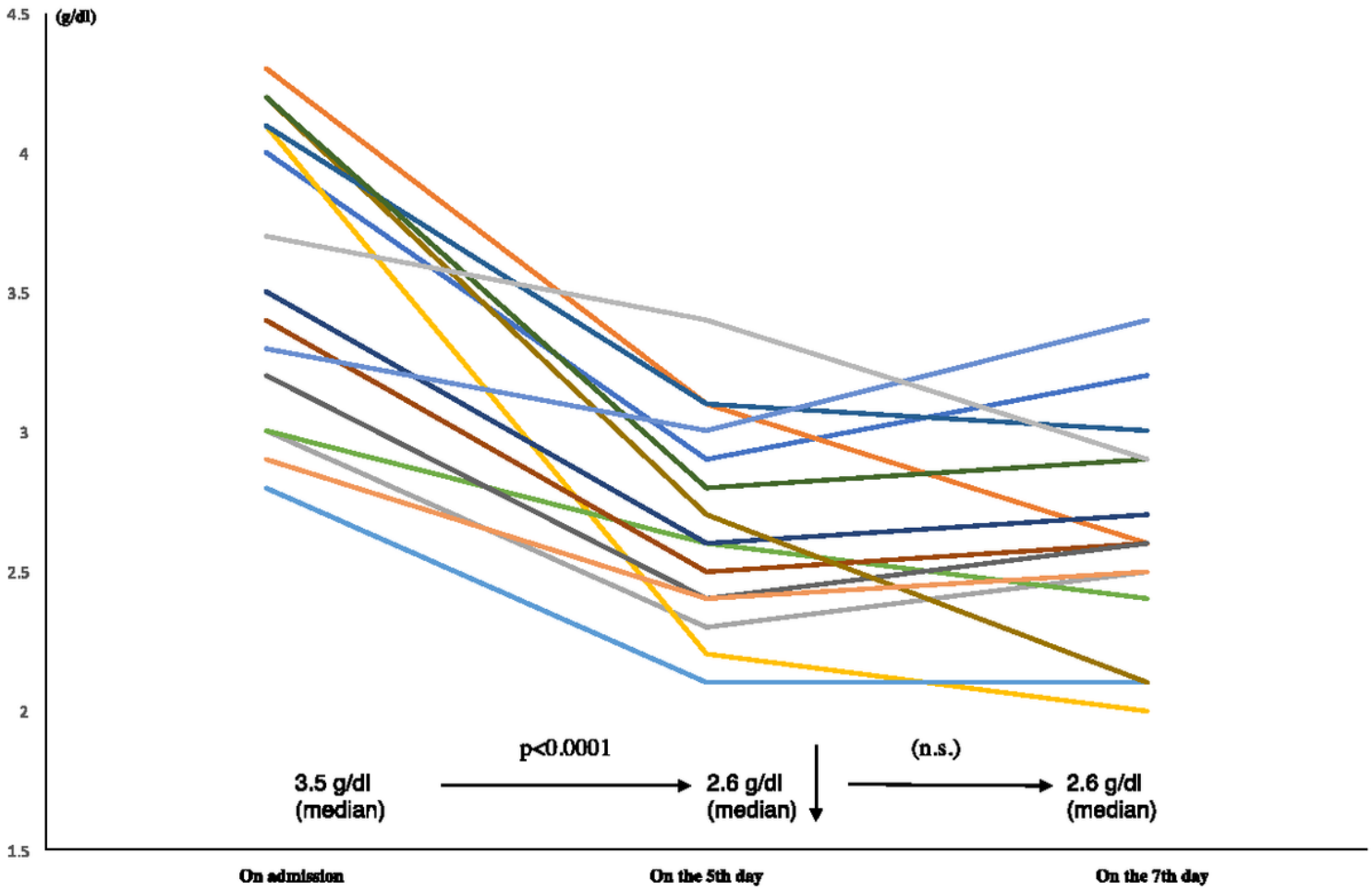

Figure 2

Serial changes of serum albumin (Alb) on admission, on the fifth day and the seventh day. As shown, a one-sided Wilcoxon signed-rank test was performed.

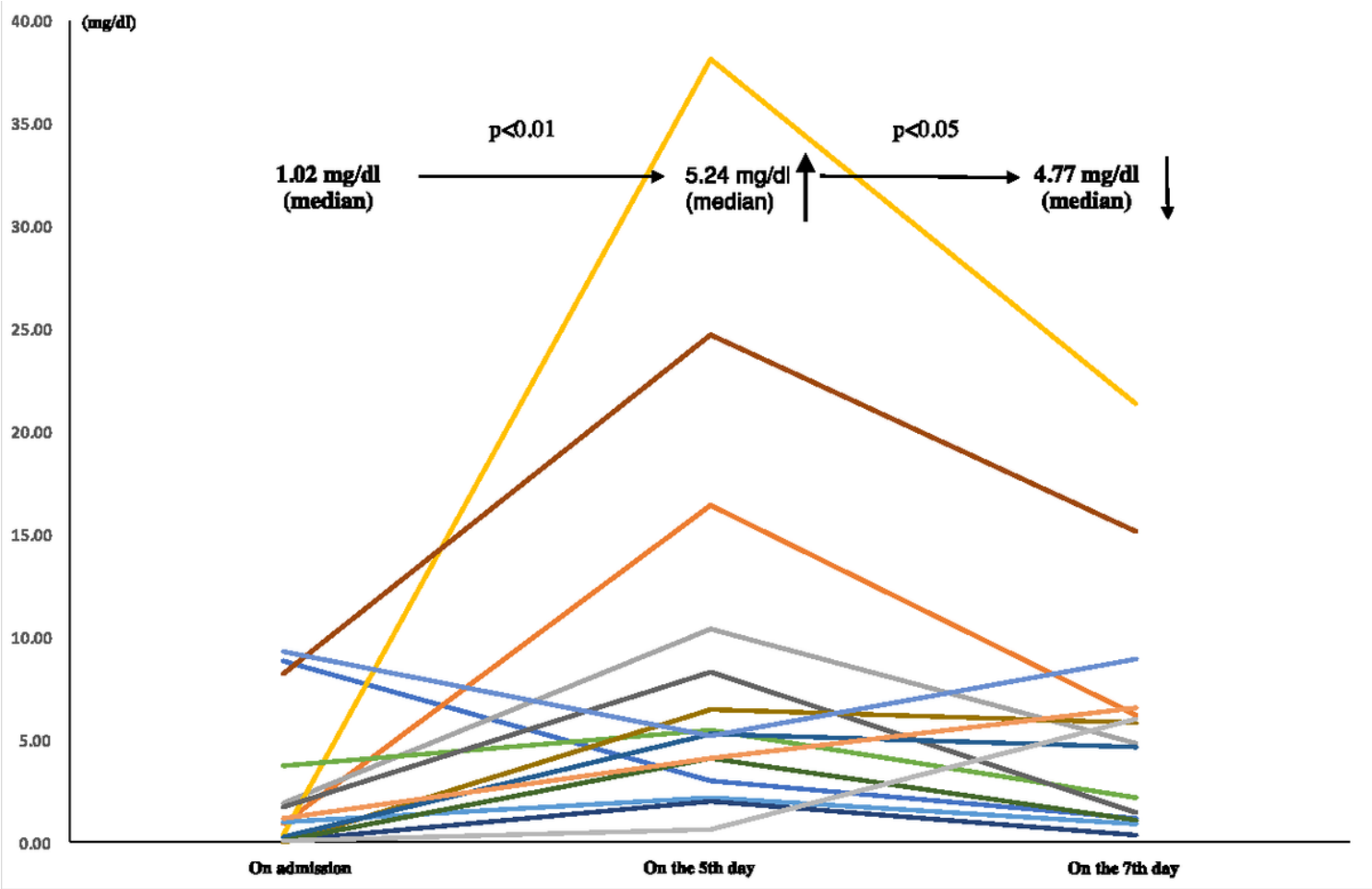

Figure 3

Serial changes of serum high sensitive c-reactive protein (CRP) on admission, on the fifth day and the seventh day. One-sided Wilcoxon signed-rank test was performed.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx