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Development of a nutritional index to evaluate the effectiveness of total parenteral nutrition during the early postoperative period after pancreaticoduodenectomy

Sung Whan Cha

The Graduate School

Yonsei University

Department of medicine

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지도교수 류 훈

이 논문을 석사 학위 논문으로 제출함

2021년 12월 30일

연세대학교 대학원

의학과

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2021년 12월 30일

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학위논문 국문 요약

췌장 십이지장 절제술 후 초기 기간 동안 경정맥영양요법의 효과를 평가하기 위한
영양 지수 개발

1935 년 Whipple에 의해 도입 된 이래, 췌장 두절 절제술은 췌장 머리, Vater의 앰플 라, 십
이지장 및 원위 공통 담관 및 일부 양성 병변과 같은 주변 골수종 암의 치료로 남아 있습니
다. PD 후, 환자는 열악한 구강 섭취를 유발하는 위장관 변화 및 영양소 분해 및 흡수에 필
요한 십이지장의 손실로 인해 영양 실조의 위험이 높습니다. 영양 실조는 급진적 환자의 열
악한 결과를 독립적으로 예측합니다 악성 간 담도 질환 수술 및 이환율, 사망률, 체류 기간
및 재정적 부담을 증가시킵니다. 수술 후 상태의 특징 인이 생리 학적 상태를 극복하기 위
해, 즉각적인 수술 기간 동안 고 칼로리 섭취의 투여가 필요하다. 더욱이, 영양 위험의 조기
발견은 조기 개입을 촉진하고 추후의 합병증을 예방하지만, 급진적 수술 후 초기 영양 상태
평가를위한 단일 금 표준 객관적인 측정은 고안되지 않았다. 영양 지원은 구강 경로를 통해
일상적으로 수행되지만 이것이 문제가 될 경우 정맥 내 총 비경 구 영양과 같은 대체 영양
보충 원이 필수적입니다. 영양 지원 전략은 지난 수십 년 동안 상당히 발전했으며 일반적으
로 수술 후 TPN이 사용 되었습니다. TPN은 효과적인 영양 지원 방법이지만, 그 사용은 중
양성 관련 혈류 감염 (CLABSI), 고혈당증과 같은 합병증의 위험과 관련이 있습니다. 간 기능
이상 및 전해질 불균형. 이러한 단점에도 불구하고, TPN은 여전히 심각한 수술 후 합병증
및 수술 전 영양 실조의 위험으로부터 환자를 구출하는 데 중요한 역할을 합니다. 특히, 14
일 이상 충분한 영양 지원을 받지 않은 환자는 합병증 및 사망률이 현저히 증가했습니다.
또한 영양 실조로 인해 근육 감소증이 발생할 수 있습니다. 따라서 이러한 열악한 결과를
피하기 위해 조기 영양 보충에 대한 적절한 적응증을 식별하는 것이 긍정적으로 필요합니
다. 여러 유형의 혈청 학적 마커 (예 : 알부민, 트랜스페린, 프리 알부민)가 영양 상태를 평가
하는 데 널리 사용되었으며 영양 실조 환자의 예후와 관련이있는 것으로 나타났습니다. 골
격근 질량, 질 및 힘. 인체 측정, 생체 전기 임피던스 분석 (BIA), 이중 에너지 X 선 흡수 측
정 (DEXA) 및 CT / MRI와 같은 몇 가지 기술을 사용하여 근육 질량을 측정 할 수 있습니
다. 이 도구들 중 CT 스캔은 근육 질량과 지방을 측정하는 가장 유효하고 정확한 수단을 제
공하며 근육 질량의 가장 정확한 물리적 특성을 측정 할 수 있습니다.

학위논문 영문 요약

Development of a nutritional index to evaluate the effectiveness of total parenteral nutrition during the early postoperative period after pancreaticoduodenectomy

Since its introduction by Whipple in 1935, pancreatic dissection has remained a treatment for cancer of surrounding myeloma, such as pancreatic head, ampulla of Vater, duodenum and distal common bile ducts, and some benign lesions. After the PD, the patient is at high risk of malnutrition due to changes in the gastrointestinal tract that cause poor oral intakes and loss of the duodenum required for nutrient decomposition and absorption. Malnourishment independently predicts the poor outcomes of radical patients. Increases surgery and return on malignant liver biliary tract diseases, mortality, duration of stay, and financial burden. In order for the characteristic of postoperative condition to overcome physiological condition, high calorie intake is required during immediate surgery. Moreover, early detection of nutritional risks promotes early intervention and prevents subsequent complications, but no single gold standard objective measurement for assessing the initial nutritional status after radical surgery is devised. Nutrition support is routinely carried out through oral pathways, but if this is a problem, alternative nutritional supplements such as total intravenous non-catholic oral nutrition are essential. Nutrition support strategies have evolved significantly over the past few decades and have generally been used postoperative TPN. TPN is an effective nutritional support method, but its use relates to the risk of complications such as centerline related blood flow infections (CLABSI) and hyperglycemia. Liver function abnormality and electrolyte imbalance. Despite these shortcomings, TPN still plays an important role in rescuing patients from serious postoperative complications and the risk of preoperative malnutrition. In particular, patients who did not receive sufficient nutrition support for more than 14 days experienced significant increases in complications and mortality. In addition, muscle loss can occur due to malnutrition. Therefore, it is positively necessary to identify appropriate adaptations for early nutritional supplementation to avoid these poor results. Several types of serum academic markers (e.g., albumin, transferrin, and free albumin) were widely used to assess nutritional status and were found to be related to the prognosis of malnourished patients. The mass, quality, and strength of skeletal muscle. Muscle mass can be measured

using several techniques, such as human measurement, biomechanical impedance analysis (BIA), dual energy X-ray absorption measurement (DEXA), and CT / MRI. Among these tools, CT scans provide the most effective and accurate measure of muscle mass and fat, and can measure the most accurate physical properties of muscle mass.

Abstract

Background: Malnutrition leads to adverse effects on the short- and long-term prognosis in patients with periampullary diseases who underwent surgery. Nutritional risk indicators based on albumin and body weight have been developed to evaluate nutritional status and nutritional therapy efficacy, but no standard objective measurement has been devised to evaluate nutritional status during the early period after pancreaticoduodenectomy (PD). Therefore, this study aimed to assess the efficacy of total parenteral nutrition (TPN) during the early postoperative period after PD.

Methods: We analyzed 28 patients with a periampullary disease - Common bile duct cancer, Ampulla of Vater cancer, pancreatic head cancer, neuroendocrine tumor, chronic pancreatitis - who have undergone PD from Jan. 1, 2012 to Dec. 31, 2016. For all the patients, TPN was administered from postoperative day (POD) 1 at 25Kcal/kg ideal body weight. Various nutritional indicators were measured such as Body mass index, nutritional risk index, protein, albumin, prealbumin, C-reactive protein. The volume of skeletal muscle area, muscle density, visceral and subcutaneous fat areas were assessed two times, preoperatively and on POD 7 by CT scan at the 3rdlumbar spine(L3)level.

Results: Average age of the 28 study subjects (18 males and 10 females) was 63.5 ± 9.7 years. Although there is no difference in BMI between preoperative result and POD 7, protein, albumin, and prealbumin levels were significantly lower POD 7 the preoperative ($p < 0.001$), but CRP was higher ($P < 0.001$), and prealbumin and CRP levels were negatively correlated ($R = -0.682$, $p < 0.01$). Muscle mass increased postoperatively ($p = 0.02$), but the amount of visceral fat decreased ($p = 0.00$). Based on

CRP, and muscle density results, muscle, visceral and subcutaneous fat masses did not change after PD.

Conclusions: In order to evaluate the nutritional status accurately after the hepato-biliary radical surgery, we suggest the muscle and fat mass measurement that can adjust the degree of inflammation during the early postoperative period.

Keywords: Pancreaticoduodenectomy, Total Parenteral Nutrition,
Nutritional Assessment, Sarcopenia

1. Introduction

Since its introduction by Whipple in 1935[1], pancreaticoduodenectomy (PD) remains the treatment of choice for periampullary carcinomas, including such as those of the pancreas head, ampulla of Vater, duodenum, and distal common bile duct, and some benign lesions. After PD, patients are at high risk of malnutrition, because of gastrointestinal tract changes that cause poor oral intake, and loss of duodenum, which is required for nutrient breakdown and absorption.[2, 3]

Malnutrition is an independent predictor of poor outcomes in patients who have undergone radical surgery for malignant hepatobiliary disease and increases morbidity, mortality, length of stay, and financial burden.[4, 5]. To overcome this physiologic condition, which is the hallmark of the postsurgical state, the administration of high caloric intake during the immediate postoperative period is necessary. Furthermore, the early detection of nutritional risk facilitates early intervention and prevents later complications, but no single gold standard objective measurement has been devised for the evaluation of nutritional status during the early

period after radical surgery.

Nutritional support is performed routinely via the oral route, but when this is problematic, alternative sources of nutritional supplementation such as intravenous total parenteral nutrition (TPN) are essential.[6] Nutritional support strategies have evolved considerably over the past decades and commonly TPN has been used postoperatively.[7]

Although TPN is an effective method of nutritional support, its use is associated with risks of complications such as central line-associated bloodstream infection, hyperglycemia, liver function abnormalities, and electrolyte imbalance. [8] Despite these shortcomings, TPN still plays a key role in the rescue of patients from severe postoperative complications and the risk of postoperative malnutrition. Notably, patients who have not received sufficient nutritional support for more than 14 days have remarkably elevated complications and mortality rates; [9], and furthermore, malnutrition can result in sarcopenia. Thus, it is positively necessary to identify appropriate indications for early nutritional supplementation to avoid these poor outcomes.

Several types of serologic markers (e.g., albumin, transferrin, prealbumin) have been widely used to evaluate nutritional status, and shown to be associated with the prognoses of malnourished patients.[10, 11] Malnutrition can cause sarcopenia which is the degenerative loss of skeletal muscle mass, quality, and strength. Several techniques, such as anthropometry, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), and CT/MRI, are available to measure muscle mass. Of these tools, a CT scan provides the most valid and precise means of measuring muscle mass and fat and can measure the most

exact physical properties of muscle mass. [12]

However, no tool has been developed to determine the efficacy of TPN administered to patients during the early postoperative period. We aimed to assess the effectiveness of TPN for the patients who are in the early postoperative period after PD.

We present the following article in accordance with the STROBE reporting checklist.

2. Material and Method

This retrospective study was conducted at a single university hospital. We analyzed 28 patients with a periampullary disease, that underwent PD from January 1, 2012 to December 31, 2016. All patients were operated upon by a single surgeon using the same procedures, which included (a) single-loop pancreatic and biliary reconstruction; (b) pancreaticojejunostomy; (c) duct-to-mucosa anastomosis; (d) internal pancreatic duct silicone stent placement, and (e) continuous suturing of pancreatic parenchyma to jejunal serosa with prolene.

For all the patients, TPN was administered from postoperative day (POD) 1. The total required calorie was calculated at 25 Kcal/kg ideal body weight as this calorie furnishes an approximate estimate of daily energy expenditure and requirements. [13] The initial target calorie that TPN provides on POD 1 was to supply 60% of the total required calories. Then, the target calorie gradually increased daily; 80% on POD 2, and 100% on POD 3.

CT scan was taken in all the patients on POD 7. And enteral feeding began when the CT scan showed no evidence of complications. The

amount of TPN administration was gradually decreased depending on the amount of oral intake. If the patients are tolerable with 20% amount of usual oral intake, the total calorie of TPN was decreased to 80% of required calorie. This gradual increase and decrease method of TPN administration was determined by our team.

Several nutritional indicators - body mass index (BMI), nutritional risk index (NRI), protein, albumin, prealbumin, and C-reactive protein (CRP) - were measured at the preoperative period and on POD 7. All the indicators in the preoperative period were examined one day before surgery. NRI was calculated as follows; $NRI = (1.519 \times \text{serum albumin, g/dL}) + \{41.7 \times \text{present weight (kg)}/\text{ideal body weight (kg)}\}$. Muscle density and muscle, visceral fat, and subcutaneous fat masses were determined using a CT scan [12] before surgery and POD 7 at the 3rd lumbar spine (L3) level. (Fig. 1) The preoperative CT scan was taken at the outpatient clinic, and the average period from the day when the CT scan was taken to surgery was 16.25 ± 5.78 days. The CT scan was obtained using a 16- or 64-section scanner (Somatom Sensation 16 or 64; Siemens Medical Solutions, Forchheim, Germany) and a section thickness 3 mm. [14]

To see whether they are affected by the inflammation, we analyzed the correlation between albumin and prealbumin, CRP and prealbumin. And the comparison of prealbumin to CRP ratio between preoperative period and POD 7 was conducted.

The difference of serum CRP level between the perioperative period and POD 7 was divided into three groups - ① less than zero square of ten ($<10^0$), ② from greater than or equal to a square of ten up to less than two square of ten ($\leq 10^1 \sim <10^2$), ③ greater or equal to two square of

ten ($\geq 10^2$). For each group, we analyzed the correlation with prealbumin, muscle mass, muscle density, visceral and subcutaneous fat.

2-1 Statistical analysis

The statistical analysis was performed using SPSS version 23, and correlation analysis using the Pearson test. The paired t test and ANOVA were used for group comparisons. Results are presented as means \pm SDs and statistical significance was accepted for p values < 0.05.

3. Results

The study subjects were 18 males and 10 females of overall average age 63.5 ± 9.7 years, and BMI 22.89 ± 3.11 kg/m². Of the 28 patients, common bile duct cancer was the most common diagnosis (46.4%) following in decreasing order by ampulla of Vater cancer, pancreatic head cancer, chronic pancreatitis, and neuroendocrine tumor. (Table 1)

NRI, protein, albumin, and prealbumin were significantly lower ($p < 0.001$), but CRP was significantly higher ($P < 0.001$) at POD 7 than preoperative period. (Table 2)

Prealbumin and albumin levels were positively correlated ($p = 0.006$) (Figure 2). But on the contrary prealbumin and CRP levels were negatively correlated ($p < 0.001$) (Figure 3), and prealbumin to CRP ratio was significantly lower on POD 7 ($p = 0.003$) (Figure 4). There was a significant difference in comparison the group divided by CRP change with prealbumin between the preoperative period and POD 7 ($p < 0.001$) (Figure 5).

Muscle mass was higher ($P=0.02$) and visceral fat was lower ($p<0.001$) on POD 7 than preoperative period, but muscle density and amount of subcutaneous fat were similar in both periods. (Figure 6). There was no significant difference in comparison between the groups divided by CRP change and muscle density, muscle mass, visceral and subcutaneous fat amount (Figure 7).

4. Discussion

Hepatobiliary and pancreatic malignancy is often associated with malnutrition, which is attributed to sustained pro-inflammatory cytokine response, poor dietary intake, and the catabolic effects of sepsis. [15, 16] As malnutrition has a negative effect on prognosis after radical surgery, adequate nutritional support is mandatory.

Various methods have been used to provide patients with sufficient nutrition during the postoperative period. The early recovery after surgery (ERAS) protocol reported that the initiation of early enteral feeding has shown to reduce complications and hospital stays, and promote earlier bowel function recovery and the resumption of normal activities. [17, 18]

However, the anatomical change of the gastrointestinal tract after surgery causes an insufficient oral intake, an additional nutritional supply is required such as enteral tube feeding or TPN to provide enough calorie.[6] The optimal means of parenteral feeding remains controversial and though numerous studies have compared the efficacy of enteral feeding and TPN, the results vary.[19-23]

Various serologic parameters have been used to estimate the nutritional statuses of patients at the postoperative period. But, these parameters

are easily influenced by environmental factors, inflammatory conditions, and drugs.[10] As shown in figure 3-5, our results verify this phenomenon. Therefore, it appears these parameters are not suitable to assess the nutritional status at immediate postoperative period because of inflammatory process in the body.

Sarcopenia is a syndrome characterized by progressive, generalized loss of skeletal muscle mass and strength, and can be diagnosed by low muscle mass and poor muscle function. Numerous studies have reported that sarcopenia is highly associated with poor outcomes, and mortality.[24-30]

Recently, sarcopenia has been identified as a poor prognostic factor for patients with pancreatic cancer, colorectal with liver metastasis, liver cirrhosis and liver transplantation.[31-34] Besides, sarcopenia is known to have negative impacts on postoperative morbidity and prognosis undergoing PD, and also it is the risk factor for postoperative pancreatic fistula which is the most fatal complication after PD.[34-36] Therefore, prevention of sarcopenia after surgery is important.

Several methods can be used to assess muscle mass, but all have advantages and disadvantages. Although CT scan measures of muscle mass provide the most reliable and accurate information, the technique is hospital-based, expensive, and time-consuming as compared with other modalities. But, as all the patients who underwent PD routinely take CT scan postoperatively to check complications, the anthropometric data can be collected without an additional charge.

To determine the effectiveness of TPN, we compared muscle mass, muscle density, and visceral and subcutaneous fat amounts measured

preoperatively and on POD 7. Our important finding was that although visceral fat amounts were reduced on POD 7, muscle mass was unaffected or even tended to increase, which can be explained that the protein sparing effect of TPN administration prevented muscle degradation. Furthermore, the maintenance or increase of muscle mass can prevent sarcopenia by appropriate TPN administration.

In order to evaluate the nutrition status accurately after PD, we suggest that CT scan-based measurement of muscle and fat mass measurements at the postoperative period. Also we suggest a prospective study to compare nutritional statuses in enteral feeding and TPN groups after PD and to investigate the effects of oral intake amounts and the timing of supplementation.

The limitations of this study include a small number of patient populations and the lack of similar research related to the effectiveness of TPN at early postoperative period after major surgery.

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Table 1. Patient characteristics

Pancreaticoduodenectomy	
Number	28
Sex (Male/Female)	18 / 10
Age	63.54 ±9.72
Body Mass index (kg/m ²)	22.89 ±3.11
Diagnosis	
Common bile duct cancer	13 (46.4%)
Ampulla of Vater cancer	9 (32.1%)
Pancreas head cancer	2 (7.2%)
Chronic pancreatitis	2 (7.2%)
Neuroendocrine tumor	2 (7.2%)

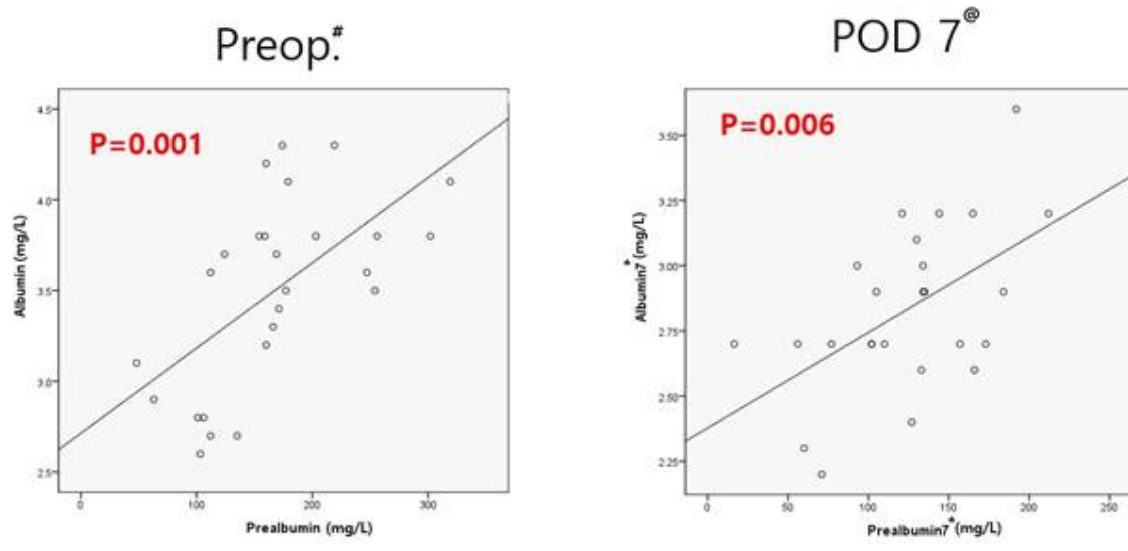
Table 2. Postoperative nutritional marker changes

	Preoperative	Postoperative day 7	p
BMI (kg/m ²)	22.98 ±3.03	22.78 ±3.35	0.282
NRI	50.27 ±7.02	48.81 ±7.32	0.001
Protein (g/dL)	6.04 ±0.62	5.38 ±0.52	<0.001
Albumin (g/dL)	3.53 ±0.52	2.84 ±0.31	<0.001
Prealbumin (mg/L)	166.87 ±68.54	123.72 ±48.36	<0.001
CRP (mg/dL)	12.23 ±19.69	74.33 ±48.85	<0.001

Figure 1. Muscle and Fat Mass measurement in PD patients



Figure 2. Correlations between prealbumin and albumin (a), and prealbumin and CRP (b) levels



Preop: Preoperative period

@ POD7: Postoperative day 7

*Albumin7 & Prealbumin 7: Serum albumin and prealbumin level on POD 7

Figure 3. Postoperative changes in prealbumin-CRP ratios

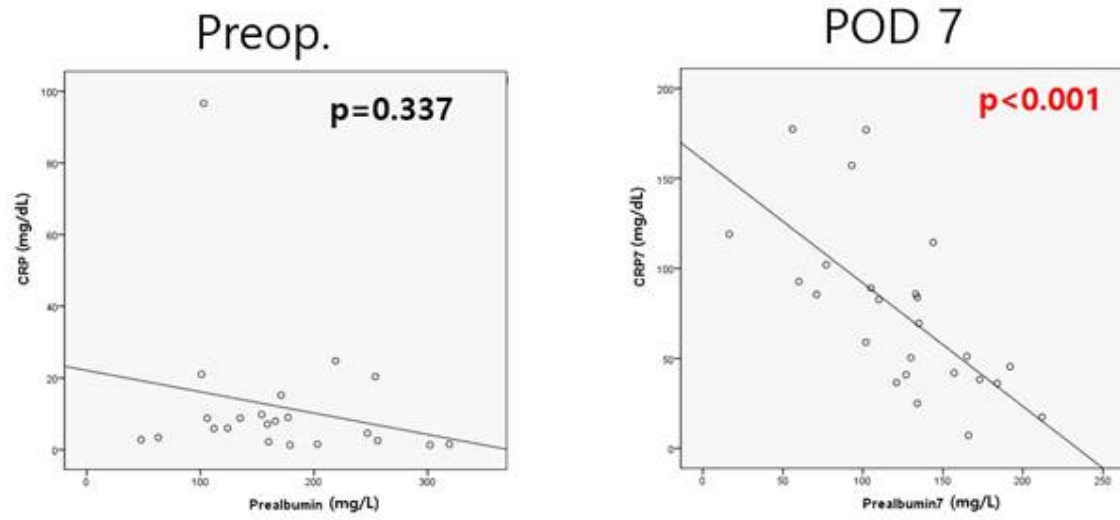


Figure 4. Comparison of prealbumin/CRP ratio. CRP, C-reactive protein.

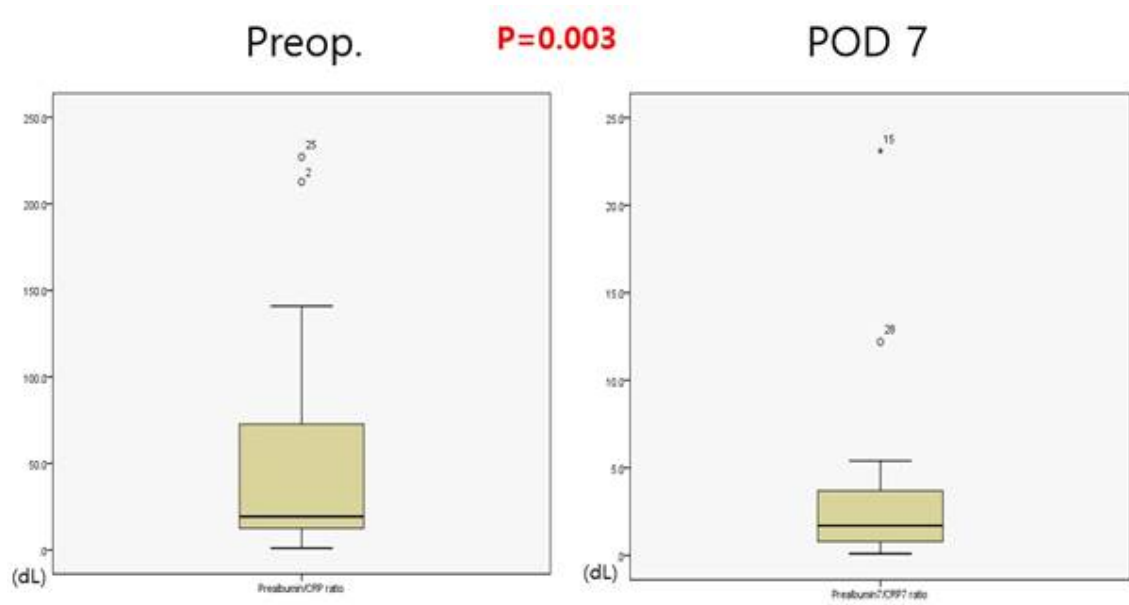
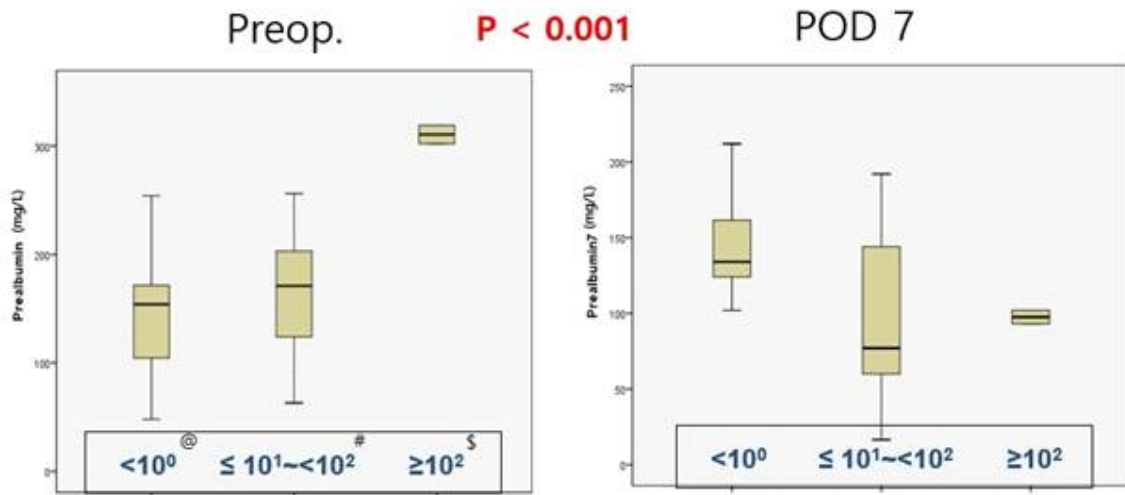


Figure 5. Variation of Prealbumin level according to the changes of CRP

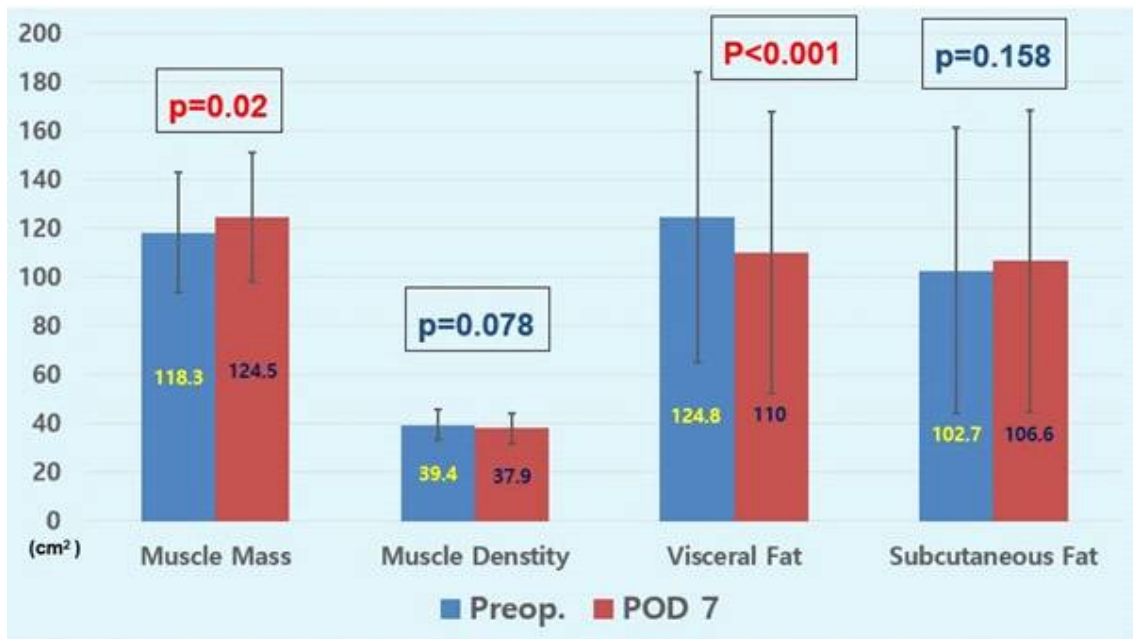


@: less than zero square of ten

#: from greater than or equal to a square of ten up to less than two square of ten

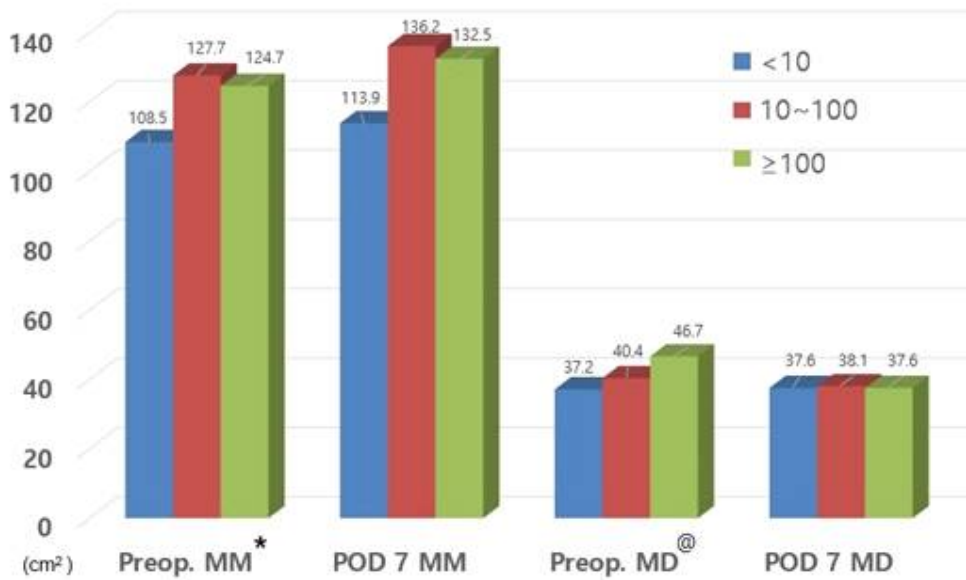
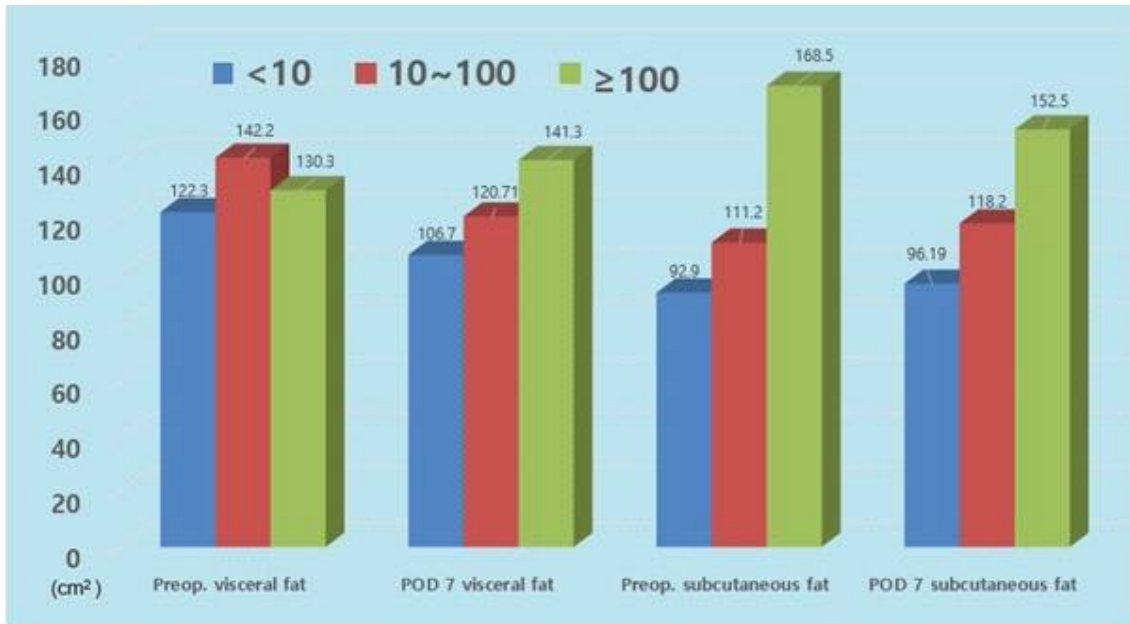
\$: greater or equal to two square of ten

Figure 6. Comparison of anthropometric parameters



Muscle mass and density, visceral and subcutaneous fat amounts were evaluated by CT scan at L3 level, and compared between preoperative period and POD 7.

Figure 7. Changes in muscle mass, muscle density, visceral and subcutaneous fat amounts with respect to CRP



*: Muscle mass

@: Muscle density