# Associations of plasma aprepitant and its *N*-dealklated metabolite with cachexia progression and clinical responses in head and neck cancer patients

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**Research Article**

**Keywords:** aprepitant, metabolite, pharmacokinetics, cachexia, CINV

**Posted Date:** April 8th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1414973/v1

# Abstract

**Purpose**: Oral aprepitant has a large interindividual variation in clinical responses in advanced cancer. This study aimed to characterize plasma aprepitant and its *N*-dealkylated metabolite (ND-AP) based on the cachexia progression and clinical responses in head and neck cancer patients.

**Methods**: Fifty-three head and neck cancer patients receiving cisplatin-based chemotherapy with oral aprepitant were enrolled. Plasma concentrations of total and free aprepitant and ND-AP were determined at 24 hours after a 3-day aprepitant treatment. The clinical responses to aprepitant and degrees of cachexia progression were assessed using a questionnaire and Glasgow Prognostic Score (GPS).

**Results**: Serum albumin level was negatively correlated with the plasma concentrations of total and free aprepitant but not ND-AP. The serum albumin level had a negative correlation with the metabolic ratio of aprepitant. The patients with GPS 1 or 2 had higher plasma concentrations of total and free aprepitant than those with GPS 0. No difference was observed in the plasma concentration of ND-AP between the GPS classifications. The plasma interleukin-6 level was higher in patients with GPS 1 or 2 than 0. The absolute plasma concentration of free ND-AP was higher in patients without the delayed nausea, and its concentration to determine the occurrence was 18.9 ng/mL. The occurrence of delayed nausea had no relation with absolute plasma aprepitant.

**Conclusion**: Cancer patients with a lower serum albumin and progressive cachectic condition had a higher plasma aprepitant level. In contrast, plasma free ND-AP but not aprepitant was related to the antiemetic efficacy of oral aprepitant.


# Introduction

Aprepitant, a highly selective antagonist of neurokinin-1 (NK1) receptor, is commonly used in combination with dexamethasone and a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting (CINV). The prophylactic use of aprepitant reduces acute and delayed CINV in 70–80% of patients receiving highly emetogenic chemotherapy [1–3]. In contrast, some patients treated with aprepitant have poor antiemetic efficacy and experience undesirable adverse effects such as hiccups, constipation, and headache [2, 4, 5]. The factors responsible for individual variations in antiemetic efficacy and adverse effects of aprepitant remain to be clarified in cancer chemotherapy.

Advanced cancer patients have a large variation in the plasma aprepitant level [6]. The oral bioavailability of aprepitant was reported to be 59–67% in healthy adults [7]. The main metabolism pathway of aprepitant is desorption of the triazolone ring by *N*-dealkylation via cytochrome P450 (CYP) 3A4 in the liver [8]. The metabolites, including *N*-dealkylated aprepitant (ND-AP), have a high affinity for the NK1 receptor as well as aprepitant *in vitro*. Plasma ND-AP has been recently reported to have a large variation in cancer patients [6, 9]. The contribution of plasma ND-AP to the antiemetic efficacy and adverse effects of aprepitant have not been assessed in cancer patients treated with oral aprepitant.

Plasma aprepitant and ND-AP must pass through the blood-brain barrier (BBB) to obtain an antiemetic effect. The BBB, characterized by impermeable endothelial cells with tight junctions, restricts the influx of a polar drug or a large size drug into the brain [10]. Aprepitant has high plasma protein binding (> 90%) [11, 12], however, no information on the protein binding properties of ND-AP is available. In addition, the contribution of specific transition transporting systems in the BBB to aprepitant and ND-AP disposition in the brain have not been revealed in humans. In ferrets, ND-AP was more distributed in the brain than aprepitant after oral aprepitant administration [13].

Advanced cancer patients tend to have hypoalbuminemia due to cancer-derived inflammation and nutritional disorders [14]. In patients with head and neck cancer, poor food intake caused by cancer progression in the throat and radiation to the oral mucosa potentially induce a decrease in serum albumin [15]. Moreover, cancer patients suffer from cachexia syndrome [16], and patients with cancer cachexia have systemic inflammation. Several clinical studies have demonstrated that the inflammatory condition caused by cancer reduces CYPs activity [17–19]. However, the relationship between plasma aprepitant or ND-AP and cachexia progression has not been evaluated in cancer patients.

Clarification of the factors determining the clinical responses to aprepitant in patients receiving highly emetogenic chemotherapy could potentially contribute to the individualization of anti-emetic therapy. The aim of this study was to characterize plasma aprepitant and ND-AP based on cachexia progression, antiemetic efficacy, and adverse effects in head and neck cancer patients.

## Methods

# Patients and blood sampling

The present study was a prospective observation study (UMIN000041069) conducted at Hamamatsu University Hospital (Hamamatsu, Japan). A total of 53 Japanese head and neck cancer patients receiving oral aprepitant (Emend Capsules, Ono Pharmaceutical Co., Ltd., Osaka, Japan), a 5-HT3 receptor antagonist, and dexamethasone for the prevention of CINV were enrolled. All patients were treated with cisplatin (> 80 mg/m$^2$)-based chemotherapy for the first time and concomitantly received aprepitant at a dose of 125 mg on day 1 before chemotherapy and 80 mg on days 2 and 3. Exclusion criteria were as follows: (1) patients who were being co-treated with potent strong CYP3A4 inducers or inhibitors including azole antifungals, macrolide antibiotics, carbamazepine, or rifampicin [20]; (2) patients who concomitantly received anti-emetic medications other than a 5-HT3 receptor antagonist and dexamethasone; (3) patients within 2 weeks of starting opioid analgesic therapy; (4) patients who were not co-treated with radiation therapy; (5) patients who had a risk of vomiting for pathophysiological reasons such as brain metastasis or disorders, gastrointestinal or infectious diseases, and Meniere's disease; (6) patients who had hepatic dysfunction (serum total bilirubin > 2.0 mg/dL); (7) patients who could not complete the questionnaire themselves; and (8) patients who could not complain of nausea and vomiting. The blood samples were collected at 24 hours after the last oral administration of aprepitant on day 4.

# Determination of plasma aprepitant and ND-AP

Plasma concentrations of total and free aprepitant and ND-AP were simultaneously determined by a liquid chromatography-tandem mass spectrometry method [6]. The calibration curves ($r > 0.99$) were 50–2500 ng/mL for total aprepitant, 20–1000 ng/mL for total ND-AP, and 5–250 ng/mL for free aprepitant and ND-AP. Their intra- and inter-assay accuracy ranges were 93.5–107.7%, while their intra- and inter-assay imprecision values were less than 8.9%. The lower limit of quantification was 50 ng/mL for total aprepitant, 20 ng/mL for total ND-AP, and 5 ng/mL for free aprepitant and ND-AP.

# Plasma exposure parameters of aprepitant and ND-AP

Variations in plasma exposures of total and free aprepitant and ND-AP were evaluated as the plasma concentration normalized with the last oral dose (80 mg) of aprepitant and body-weight. Absolute plasma concentrations of total and free aprepitant and ND-AP were used for analysis of their relationships with clinical responses. The plasma free fraction proportion (%) of aprepitant and ND-AP were calculated by dividing the free concentration by the total concentration to obtain the percentage. The aprepitant metabolism was estimated by the total concentration ratio of ND-AP to aprepitant as the metabolic ratio.

# Evaluation of cachexia progression

The degree of cachexia progression was assessed by the inflammation-based Glasgow Prognostic Score (GPS), which has been reported to predict the degree of prognosis and cachexia [21]. The GPS was determined by combining serum C-reactive protein (CRP) and albumin levels. The GPS ranges were from 0 to 2; patients with both high CRP (> 1.0 mg/dL) and low albumin (< 3.5 g/dL) level were assigned a score of 2, whereas those with either high CRP or low albumin level alone were assigned a score of 1. Patients with normal CRP and albumin levels were assigned a score of 0. Serum albumin and CRP were measured by the bromocresol purple method and latex nephelometry, respectively. The plasma IL-6 level was measured using an enzyme-linked immunosorbent assay kit (Legend Max Human IL-6 ELISA Kit, BioLegend Inc., San Diego, CA, USA).

# Evaluation of clinical responses

The incidences of CINV and adverse effects including headache, constipation, and hiccups were monitored using a questionnaire (Online Resource 1) during the first week after starting the chemotherapy. The acute and delayed phases were defined as the observation period from 0 to 24 hours and from 24 to 168 hours, respectively. For the evaluation of nausea, the dates of the nausea and the amount of food intake were obtained from the questionnaire and medical records. For the evaluation of vomiting, both the questionnaire and medical records were used to confirm the number of times a patient vomited in a day. The severities of nausea, vomiting, and adverse effects were assessed by the Common Terminology Criteria for Adverse Events version 4.0.

# Statistical analysis

The correlations between the serum levels of albumin or CRP and plasma exposure parameters of aprepitant and ND-AP were evaluated using the Spearman rank-order correlation test. The differences in the plasma exposure parameters of aprepitant and ND-AP between the GPS classification (0, non-cachexia and 1 or 2, pre-cachexia or cachexia) were evaluated by the Mann-Whitney *U* test. The correlations between the absolute plasma concentrations of total and free aprepitant and ND-AP and the incidence of CINV were also analyzed using the Mann-Whitney *U* test. The cut-off value of ND-AP to prevent chemotherapy-induced nausea was determined using the receiver operating characteristic (ROC) curve. All values are given as the median and interquartile range (IQR) unless otherwise indicated. A *P*-value of less than 0.05 was regarded as statistically significant. These statistical analyses were performed using IBM SPSS statistics ver. 25 (IBM Japan Ltd., Tokyo).

## Results

# Study population

Table 1 shows the patient characteristics. The study population consisted of 47 males and 6 females. The median total protein and serum albumin levels were 6.2 g/dL and 3.7 g/dL, respectively. The patients had pharyngeal cancer (n = 27), tongue cancer (n = 10), maxillary sinus cancer (n = 4), floor of mouth cancer (n = 4), and other types of head and neck cancer (n = 8). Cancer stages 1 to 4 were diagnosed in 3, 2, 11, and 37 patients, respectively. The patients had been receiving cisplatin (> 80 mg/m$^2$) plus a radiation regimen (n = 49), or superselective intra-arterial cisplatin (> 80 mg/m$^2$) with concomitant radiation (n = 4).

# Plasma aprepitant and ND-AP

The median plasma concentrations of total and free aprepitant were 656 (IQR, 363–901) and 27.2 (IQR, 20.3–35.9) ng/mL per mg/kg, while those of total and free ND-AP were 208 (163–333) and 10.3 (7.1–21.1) ng/mL per mg/kg, respectively. The free fractions of aprepitant and ND-AP in plasma were 5.0% (IQR, 3.5–6.2%) and 4.9% (4.0–8.1%), respectively. The median and IQR of the metabolic ratio of aprepitant were 0.40 and 0.21–0.68, respectively.

# Relationship with serum albumin and CRP

The serum albumin level was negatively correlated with the plasma concentrations of total and free aprepitant ($r_s$ = − 0.493, $P$ = 0.002 and $r_s$ = − 0.472, $P$ = 0.003, respectively). The serum albumin level had no correlation with the plasma concentrations of total and free ND-AP ($r_s$ = 0.103, $P$ = 0.544 and $r_s$ = − 0.079, $P$ = 0.641, respectively) (Fig. 1). No correlations were observed between the serum albumin level and the plasma free fraction proportion of aprepitant ($r_s$ = 0.140, $P$ = 0.410) and ND-AP ($r_s$ = − 0.231, $P$ = 0.170). The serum albumin level was positively correlated with the metabolic ratio of aprepitant ($r_s$ = 0.476, $P$ = 0.003). The serum CRP level had no correlation with the plasma exposure parameters of aprepitant and ND-AP (Online Resource 2).

# Relationship with cachexia progression

In the classification by cachexia progression, 37, 10, and 6 patients had GPS 0, 1, and 2, respectively (patient characteristics are shown in Online Resource 3). Figure 2 shows the comparison of the plasma concentrations of total and free aprepitant and ND-AP between the patients with GPS 0 and those with GPS 1 or 2. The patients with GPS 1 or 2 had a higher plasma concentration of total and free aprepitant than the patients with GPS 0 ($P = 0.014$ and $P = 0.005$, respectively). No differences were observed in the plasma concentrations of total and free ND-AP between the GPS classifications ($P = 0.670$ and $P = 0.274$, respectively). The metabolic ratio of aprepitant was not different between the GPS 0 and 1 or 2 patients ($P = 0.088$). The plasma IL-6 level was significantly higher in patients with GPS 1 or 2 (median, 7.66; and IQR, 4.30–11.7 pg/mL) than 0 (3.58 and 2.53–5.16 pg/mL) ($P = 0.023$).

# Antiemetic efficacy and incidence of adverse effects

Twenty-two patients did not develop nausea during the observation period. Figure 3 shows the number of patients with nausea on each day. Three and 30 patients experienced nausea in the acute and the delayed phase, respectively. Four and 26 patients were defined as grade 1 and 2, respectively. No patient had chemotherapy-induced vomiting during the observation period. Headache, constipation, and hiccups were reported by 10, 23, and 26 patients during the observation period, respectively. All patients were considered to be equivalent to grade 1 adverse effects; none of the patients were considered grade 2 or higher.

# Pharmacokinetic factors related to clinical responses

No differences were observed in the plasma absolute concentrations of total and free aprepitant between the patients with and without delayed nausea ($P = 0.139$ and $P = 0.220$, respectively) (Fig. 4). The plasma absolute concentration of total ND-AP also did not differ between the patients with and without delayed nausea ($P = 0.121$). In contrast, the plasma absolute concentration of free ND-AP was higher in patients without than with delayed nausea ($P = 0.017$). In the ROC analysis for chemotherapy induced nausea, the area under the curve of absolute free ND-AP was 0.751 (95% confidence interval, 0.591–0.911). The plasma absolute concentration of free ND-AP concentration to determine the occurrence of chemotherapy-induced nausea was less than 18.9 ng/mL (sensitivity for 0.733, specificity for 0.783). No difference was observed in the incidence of nausea in the patients with GPS 0 and with GPS 1 and 2. Adverse effects were not associated with any absolute plasma aprepitant and ND-AP concentrations (Online Resource 4).

# Discussion

The present prospective study investigated the associations of plasma aprepitant and its metabolite with cachexia progression, antiemetic efficacy, and adverse effects in oral aprepitant-treated head and neck cancer patients. Our findings suggest that these head and neck cancer patients who had a progressive cachectic condition have elevated plasma aprepitant. In contrast, elevated plasma free ND-AP reduces

the incidence of delayed nausea caused by high-dose cisplatin-based chemotherapy. To the best of our knowledge, this is the first report to characterize plasma aprepitant and ND-AP from the viewpoint of cachexia progression and antiemetic efficacy in a clinical setting.

The interindividual variation in plasma concentration of total aprepitant was similar to that of total ND-AP based on their IQR values. In contrast, plasma free ND-AP was more variable than plasma free aprepitant in the present population. A previous study also showed similar interindividual variability in plasma total aprepitant in a different population [22]. The plasma protein binding rate of aprepitant was more than 90% [11, 12], whereas that of ND-AP has not been reported. In the present study, the free fraction proportion of ND-AP also had a larger interindividual variability. Cancer-related factors potentially contribute to the variability in plasma free ND-AP.

A lower serum level of albumin was negatively associated with the higher plasma concentrations of total and free aprepitant, but not ND-AP in this study. In contrast, the free fraction kinetics and metabolism of aprepitant were only slightly associated with the serum albumin level. Patients with cancer, especially head and neck cancer, tend to suffer from hypoalbuminemia due to undernutrition caused by parenteral feeding [15]. Inadequate oral intake with supplemental parenteral nutrition was present in 63% of the patients in our population. Our data indicate that albumin dynamics and poor oral intake may be indirectly associated with oral aprepitant clearance. The oral bioavailability of aprepitant was reported to be approximately 60% [11]. Cytotoxic chemotherapy or intestinal edema caused by low serum albumin may lead to a higher absorption of aprepitant because of intestinal barrier breakdown. Other cancer-related factors may also be involved in the pharmacokinetic variation of aprepitant and ND-AP.

The inflammatory marker and serum CRP levels had no associations with the plasma aprepitant and ND-AP levels in the present study population. Inflammation reduces CYP3A4 activity and the oral clearance of CYP3A4-substrate drugs [23, 24]. However, the inflammatory state based on serum CRP did not have a direct correlation to plasma aprepitant. Cancer-related inflammation is responsible for the reduction of CYP3A4 activity through a complex mechanism [25, 26]. The present patients had a low total protein level (median level, 6.2 g/dL). Our data suggest that the alteration of serum protein mobilization during cancer progression affects the clearance of plasma aprepitant in advanced cancer patients.

Cancer patients with progressive cachexia had high plasma concentrations of total and free aprepitant in this study. Several studies have demonstrated that the progression of cachexia results in reduced CYPs activity [17–19, 27]. The present cancer patients with progressive cachexia tended to have a lower metabolic ratio of aprepitant. Aprepitant is metabolized predominantly by CYP3A4 [8], while CYP3A5 was not involved in aprepitant metabolism using recombinant enzymes (Online Resource 5). Our previous report also demonstrated that the CYP3A5 genotype did not alter the plasma aprepitant level [22]. These data suggest that cachexia progression increases plasma aprepitant through the reduction of CYP3A4 activity.

Our cancer patients with progressive cachexia had a higher plasma level of IL-6. IL-6 is a pro-inflammatory cytokine that causes cachexia and is directly involved in the reduction of CYP3A4 activity

[28]. In the present population, the median value of plasma IL-6 in patients with GPS 1 or 2 was 7.7 pg/mL. Diagnostic criteria for cachexia in adults include a serum IL-6 level of more than 4 pg/mL [29]. The half maximal inhibitory concentration ($IC_{50}$) of CYP3A4 activity by IL-6 was reported to be 8.3 pg/mL [30]. CYP3A4 activity may be suppressed in our study population. In addition, serum IL-6 promotes systemic protein degradation and release through cortisol and catecholamine secretion [31]. Our data suggest that plasma aprepitant is elevated via plasma IL-6 in patients with progressive cachexia.

The antiemetic effect of aprepitant was strongly associated with the absolute plasma concentration of free ND-AP but not aprepitant in this study. The $IC_{50}$ of aprepitant for the NK1 receptor was 0.1 nmol/L, while that for ND-AP was 0.5 nmol/L [11]. In plasma, the free concentration of aprepitant was similar to that of ND-AP. A higher distribution of ND-AP compared to aprepitant to brain was observed in ferrets [13]. These data support that the brain concentration of ND-AP is higher than that of aprepitant, indicating a higher inhibitory activity against brain NK1 receptors. Although most patients had a plasma concentration of total aprepitant above 100 ng/mL, which occupies more than 90% of the NK1 receptors in the brain [32], nausea occurred in approximately 50% of the patients in the present study. Aprepitant is a substrate of P-glycoprotein [33], whereas if ND-AP is also a substrate remains unknown. Since ND-AP with its detriazolone ring is structurally more basic and more likely to become a cation, it can more easily cross the BBB. The antiemetic effect of oral aprepitant may be determined by plasma ND-AP and its degree of brain migration.

The incidences headache, constipation, and hiccups were 21%, 48%, and 57%, respectively. In earlier studies using a regimen including aprepitant, the incidences of headache, constipation, and hiccups were 4–15%, 12–43%, and 10–33%, respectively [34–37]. The incidences of headache and constipation were similar to these earlier studies, while that of hiccups was higher. Cisplatin, which was administered to the enrolled patients, frequently induces hiccups [38]. No association was observed between the plasma absolute concentrations of free aprepitant or ND-AP and the adverse effects observed. To date, few reports have been published on the association between plasma aprepitant and adverse effects. Radiation therapy in addition to any concomitant drugs potentially had a positive impact on the occurrence of adverse effects in our study population.

The present study has several limitations that should be addressed. First, we enrolled head and neck cancer patients who received high-doses of cisplatin. The type of cancer did not alter the plasma aprepitant level in a previous study [22]. Patients who had moderate or severe hepatic dysfunction were not included. Application of our findings to a population without high-dose cisplatin-based chemotherapy or with hepatic dysfunction should be undertaken with care. Second, cachexia was assessed using GPS. Inflammation-based GPS classification potentially differs from symptom-based classification [39]. Inflammation-based GPS 0 or 1 is classified as pre-cachexia in the symptom-based classification. The impact of the early stage of cachexia on plasma aprepitant can be evaluated using GPS classification. The GPS could be partially substituted for a clinical symptom-based cachexia score [40]. Cachexia scoring methods may not make a major impact on our findings. Third, the present study assessed the drug concentration at a single point on day 4. Since the plasma aprepitant level at 24 hours after the last

dosing is considered to have reached the elimination phase, the observed plasma concentration reflects the drug exposure. Further studies, including systemic drug exposure analyses, would lead to better understanding of the interindividual variations in clinical responses to aprepitant.

Although cancer cachexia raised the plasma aprepitant level in this study, the clinical implication of plasma aprepitant monitoring and cachexia scoring remains to be fully clarified. Cancer cachexia had no impact on plasma free ND-AP. However, the clinical implications of plasma free ND-AP monitoring during the first cycle would enable clinicians to make a decision on additional drug dosing for patients who are predicted to respond inadequately. Based on a plasma free ND-AP level of less than 18.9 ng/mL, the additional dosing of aprepitant on days 4 and 5, or other antiemetic drugs such as olanzapine can be prophylactically prescribed during the subsequent cycle. The patient factors that can determine the plasma free ND-AP level may allow us to predict the development of CINV before starting anticancer treatment.

# Conclusions

Cancer patients with a lower serum albumin level and progressive cachectic condition had higher plasma aprepitant levels. In contrast, plasma free ND-AP but not aprepitant was associated with the antiemetic efficacy of oral aprepitant.

# Abbreviations

NK1, neurokinin-1; 5-HT3, 5-hydroxytryptamine-3; CINV, chemotherapy-induced nausea and vomiting; CYP, cytochrome P450; ND-AP, N-dealkylated aprepitant; BBB, blood-brain barrier; GPS, Glasgow Prognostic Score; CRP, C-reactive protein; IL-6, interleukin-6; ROC, receiver operating characteristic; IQR, interquartile range; $IC_{50}$, half maximal inhibitory concentration

# Declarations


### ACKNOWLEDGMENTS

This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI grant number JP20H01018 and JP21H04186.


### Consent to participate

Informed consent was obtained from all individual participants included in the study.

### Consent for publication

Not applicable


### Funding

Yusuke Suzuki received financial support from the Japan Society for the Promotion of Science (JSPS) (KAKENHI, Grant Number JP20H01018 and JP21H04186).

### Competing interests

The authors declare there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethics approval

The present study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (17-102) and was conducted in accordance with the Declaration of Helsinki. Written consent obtained from each patient after explaining the purpose of the study and other information.

### Code availability

Not applicable

### Author contributions

Yusuke Suzuki and Takafumi Naito conceptualized the study with input from Junichi Kawakami. Yusuke Suzuki funded the study. Yusuke Suzuki and Kaito Shibata recruited patients and performed blood sampling with assistance from Seiji Hosokawa. Seiji Hosokawa evaluated clinical symptoms. Yusuke Suzuki and Kaito Shibata curated drug and serum marker results and analyzed and interpreted data with assistance of Takafumi Naito. Yusuke Suzuki and Takafumi Naito wrote the manuscript and all coauthors reviewed and contributed to the manuscript.

### Availability of data and materials

The data that support the findings of the present study are available from the corresponding author upon reasonable request.

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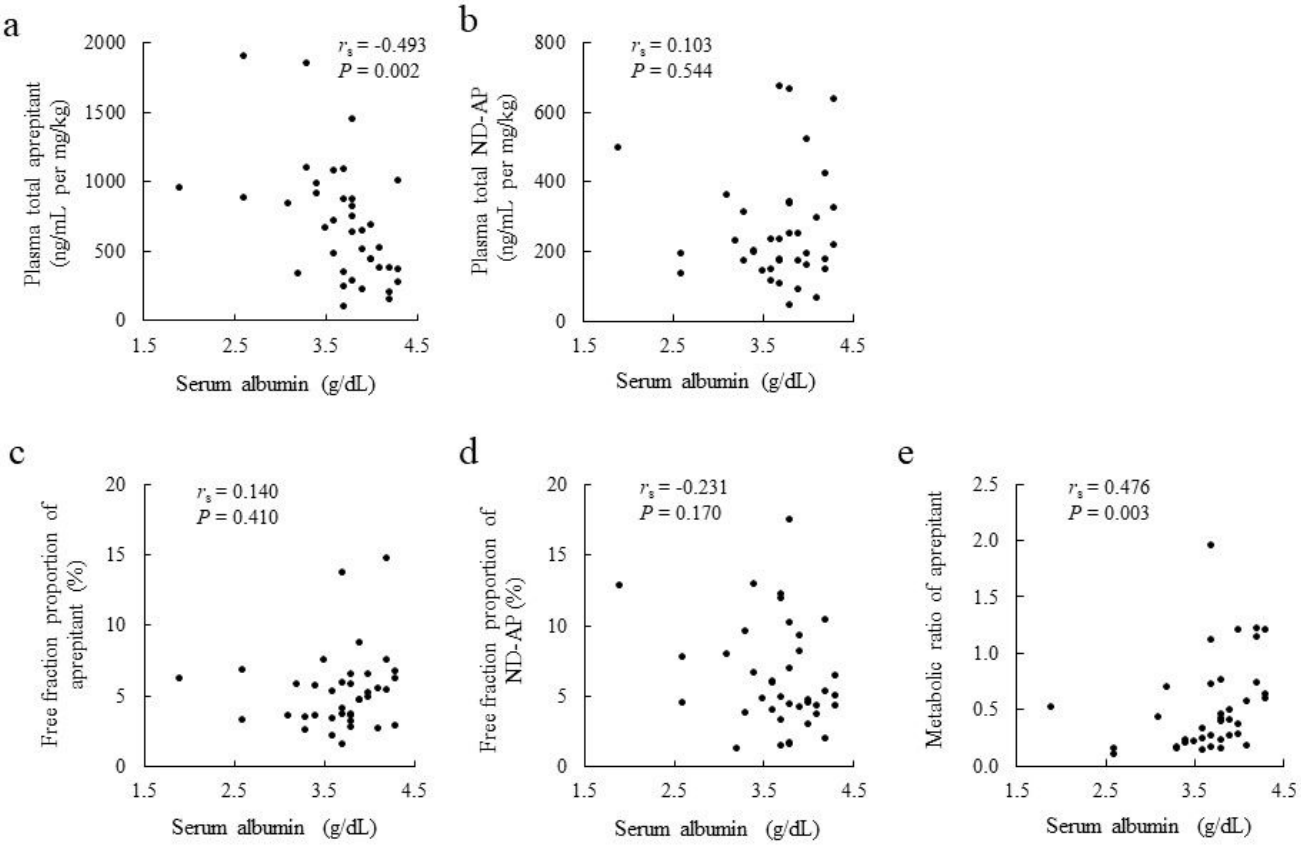
# Table

**Table 1** Patient characteristics in the study population

| | |
|---|---|
| Gender, male/female | 53, 47/6 |
| Age, years | 64 (57–68) |
| Body weight, kg | 54.5 (49.0–61.4) |
| Body mass index, kg/$m^2$ | 20.6 (18.6–21.9) |
| Total protein, g/dL | 6.2 (5.9–6.6) |
| Serum albumin, g/dL | 3.7 (3.5–3.9) |
| Serum creatinine, mg/dL | 0.69 (0.61–0.80) |
| Blood urea nitrogen, mg/dL | 16.4 (13.4–17.9) |
| Estimated glomerular filtration rate, mL/min/1.73 $m^2$ | 89 (74–100) |
| Total bilirubin, mg/dL | 0.6 (0.4–0.9) |
| Aspartate aminotransferase, IU/L | 20 (17–29) |
| Alanine aminotransferase, IU/L | 25 (16–40) |
| Alkaline phosphatase, IU/L | 190 (162–249) |
| Serum C-reactive protein, mg/dL | 0.08 (0.03–0.23) |
| Cancer type | |
| Pharyngeal cancer | 27 |
| Tongue cancer | 10 |
| Maxillary sinus cancer | 4 |
| Floor of mouth cancer | 4 |
| Ear canal cancer | 3 |
| Ethmoid sinus cancer | 2 |
| Upper gingival cancer | 2 |
| Sphenoid sinus cancer | 1 |
| Cancer stages, 1/2/3/4 | 3/2/11/37 |
| Regimen of chemotherapy | |
| Cisplatin with radiation | 49 |
| Superselective intra-arterial cisplatin with concomitant radiation | 4 |

Data are expressed as the median and interquartile range in parentheses.

# Figures

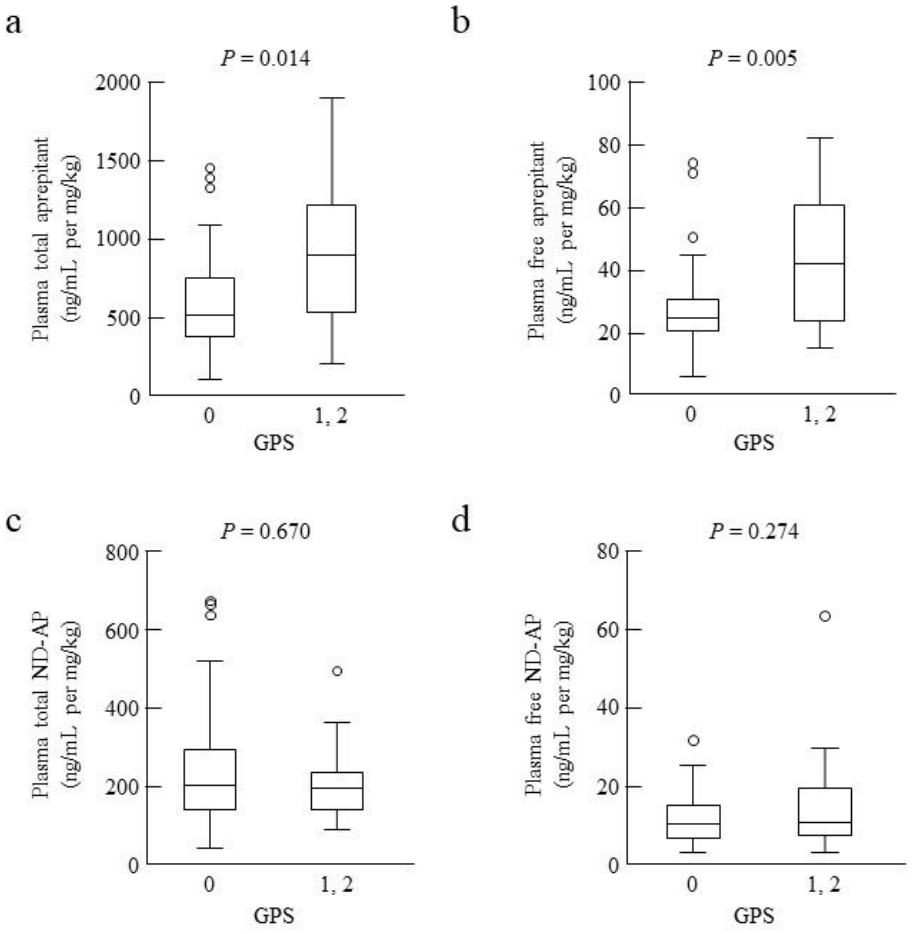



## Figure 1

Correlations between the serum albumin and plasma concentration parameters of aprepitant in cancer patients

Plasma concentrations of total aprepitant (**a**) and total *N*-dealkylated aprepitant (ND-AP) (**b**). Free fraction proportions of aprepitant (**c**) and ND-AP (**d**). Metabolic ratio of aprepitant (**e**).

The correlations were evaluated using the Spearman rank-order correlation test




## Figure 2

Comparison of the plasma total and free aprepitant and *N*-dealkylated aprepitant (ND-AP) concentrations between the Glasgow Prognostic Score (GPS)

Plasma concentrations of total aprepitant (**a**), free aprepitant (**b**), total ND-AP (**c**), free ND-AP (**d**). Statistical analysis was conducted using the Mann-Whitney *U* test

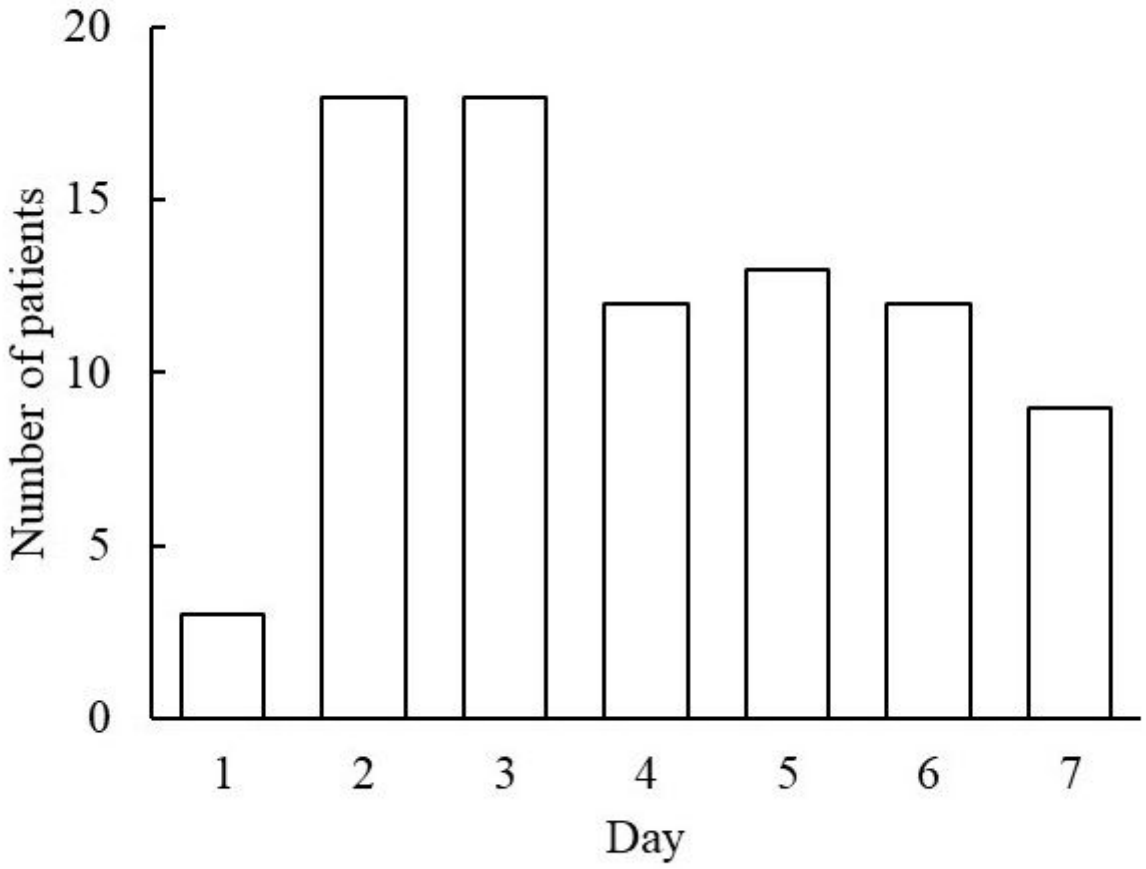



**Figure 3**

The number of patients with nausea on each day after starting chemotherapy

All patients were treated with cisplatin (> 80 mg/$m^2$)-based chemotherapy for the first time and concomitantly received aprepitant at a dose of 125 mg on day 1 before chemotherapy and 80 mg on days 2 and 3 in combination with a 5-hydroxytryptamine-3 receptor antagonist and dexamethasone

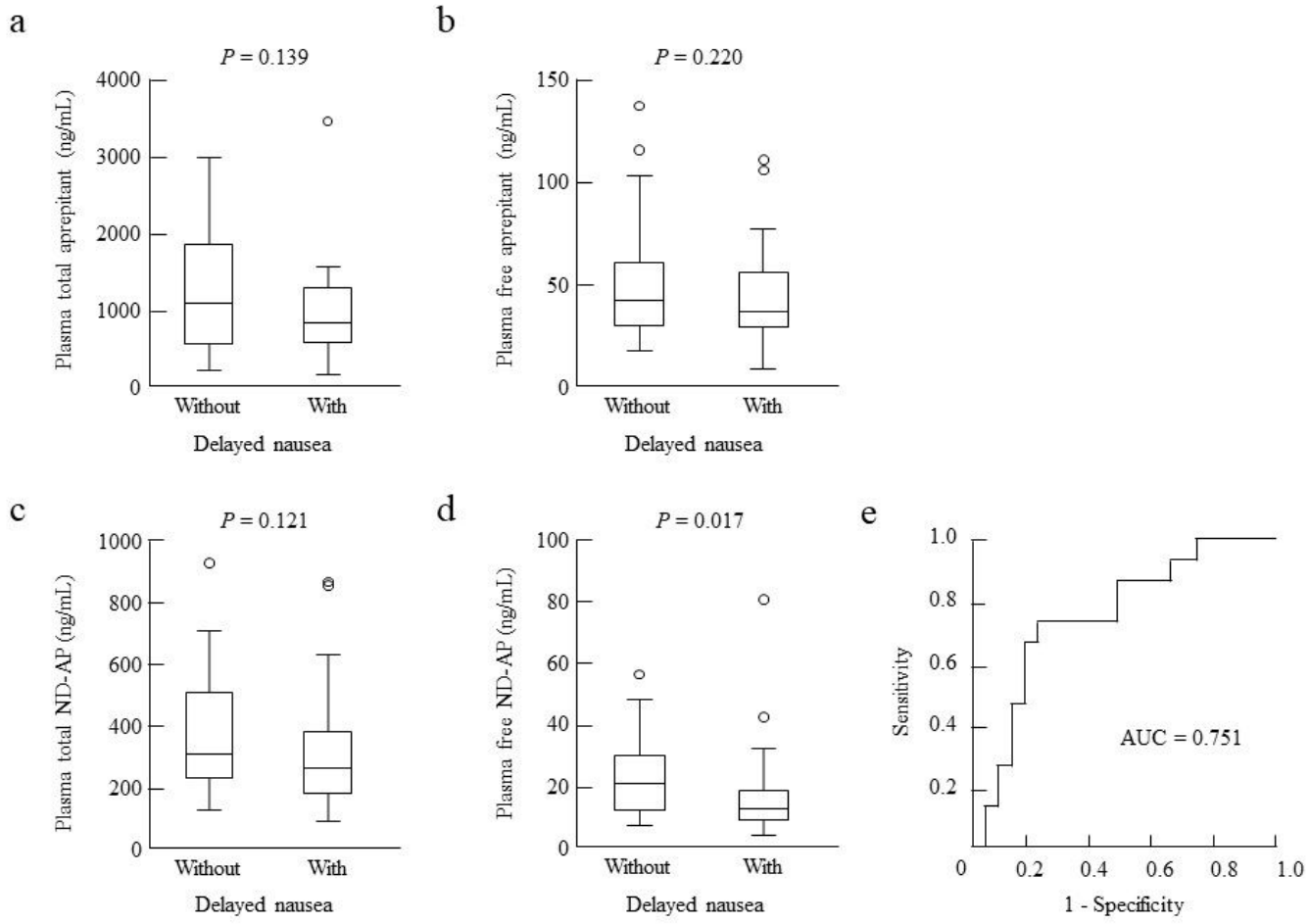



**Figure 4**

Comparison of the plasma concentrations of total and free aprepitant and *N*-dealkylated aprepitant (ND-AP) between the patients without and with delayed nausea

Plasma concentrations of total aprepitant (**a**), free aprepitant (**b**), total ND-AP (**c**), free ND-AP (**d**). Receiver operating characteristic (ROC) curve for chemotherapy-induced nausea (**e**). Statistical analysis was performed using the Mann-Whitney *U* test

AUC indicates area under the curve

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