**ORIGINAL**

# Potential effect of Ninjin'yoeito on the postoperative state of hepatectomy in a naturally aged mouse model of frailty

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**Abstract : Background : The number of elderly patients with frailty who require hepatectomy is increasing. This study aimed to investigate the effect of Ninjin'yoeito (NYT) on the post-hepatectomy state in naturally aged frailty model mice. Methods : Seventy-two-week-old mice were subjected to 70% partial hepatectomy and then divided into an NYT-treated group and a control group. Mice were sacrificed immediately (0 hours) or 24 or 48 hours after hepatectomy. Body weight, grip strength, endurance, and survival duration were investigated. Furthermore, liver function was assessed, and mRNA expression was measured using reverse-transcription PCR. Results : The body weight tended to be higher in the NYT group than in the control group 24 hours after hepatectomy ($p=0.09$). The grip strength was significantly stronger in the NYT group before and 48 hours after hepatectomy ($p<0.05$). Although survival time was slightly prolonged in the NYT group, there was no significant difference between the two groups. *HMGB1* mRNA expression in the liver was significantly suppressed in the NYT group compared with that in the control group at 24 and 48 hours after hepatectomy ($p<0.05$). Conclusions : NYT may affect the postoperative state, including body weight and motor function, in aged model mice. Suppression of HMGB1 might affect postoperative survival. J. Med. Invest. 72 : 245-251, August, 2025**

***Keywords*** **:** *Ninjin'yoeito, aged mice, hepatectomy, frailty*

## INTRODUCTION

The life expectancy is increasing in many countries. In Japan, over 37 million people are aged over 65 years, comprising 28.4% of the total population (1). Because of the aging of society, management of malignancy in elderly patients has become a global clinical issue (2). Aging is related to physiological changes, such as mitochondrial dysfunction, elevation of inflammatory or pro-inflammatory cytokines, and impairment of physical function, which are correlated with frailty (3-5). Frailty is a geriatric and multidimensional syndrome associated with increasing vulnerability and instability that can be distinguished from aging or disability alone (3). Because of developments in surgical techniques and postoperative management, the number of elderly individuals who receive surgery has been increasing. However, frailty is correlated with long hospitalization and mortality partially because of functional decline (6, 7). We previously reported that frailty itself is an independent prognostic factor after hepatectomy in elderly patients with hepatocellular carcinoma (2) or colorectal liver metastasis (8). Therefore, development of appropriate strategies for elderly frail patients to improve short- and long-term outcomes after hepatectomy is an urgent issue.

Ninjin'yoeito (NYT), a Japanese traditional herbal medicine, has been used for recovery from various disorders, such as malaise, fatigue, cold sensations, and appetite loss. NYT is a multicomponent drug that includes twelve herbs and plant products : ginseng, rehmannia root, angelica root, peony root, polygala root, astragalus root, atractylodes rhizome, poria sclerotium, cinnamon bark, citrus unshiu peel, glycyrrhiza, and schisandra fruit (9-11). NYT has been reported to increase muscle mass and strength in patients with frailty and in patients during rehabilitation (12). NYT has also been reported to improve muscle-related complications in mice with chronic obstructive pulmonary disease and cancer (13, 14). Furthermore, several components of NYT have antioxidant properties (15-17), and NYT has been reported to show antioxidant effects (18). This influence of NYT may have clinical effects after hepatectomy, especially in elderly patients because oxidative stress is related to delayed liver regeneration and post-surgical mortality (19).

The aim of this study is to investigate the effect of NYT on the post-hepatectomy state in a naturally aged mouse model of frailty.

## METHODS

### *Experimental frail hepatectomy model and NYT administration*

Seventy-two-week-old C57BL/6J mice (The Jackson Laboratory Japan, Yokohama, Japan) were used for all experiments. Mice were allowed free access to water and a basal MF diet (Oriental Yeast, Tokyo, Japan). They were housed with a temperature of 23±2°C, relative humidity of 55±5%, and 12-hour light/12-hour dark cycle with lights on from 0800 to 2000 hours (8 am to 8 pm) daily. The mice were divided into two groups : an NYT group (basal MF diet + NYT) and a control group (basal MF diet only). NYT granules were manufactured under strictly

Abbreviations :
NYT : Ninjin'yoeito, AST : aspartate aminotransferase, ALT : alanine aminotransferase, T-Bil : total bilirubin, GAPDH : glyceraldehyde 3-phosphate dehydrogenase, IL6 : interleukin-6, IL1B : interleukin-1β, HMGB1 : high mobility group box 1

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controlled conditions (Tsumura & Co., Tokyo, Japan). NYT contains twelve herbs and plant products as described above. In the NYT group, 3% NYT was mixed into the basal MF diet (18) and administered orally every day from 1 week before hepatectomy until the end of the experiment. Mice were subjected to 70% partial hepatectomy (20) and were sacrificed immediately (0 hours) or 24 or 48 hours after hepatectomy. The body weight, grip strength, and motor function were measured immediately before and 24 and 48 hours after hepatectomy. The survival rate was also evaluated (n=20 in each group). An MK380M instrument (Muromachi Kikai Co., Ltd., Japan) was used to measure grip strength. Mice were assessed for endurance using a rotarod test (MK-600, Muromachi Kikai Co., Ltd., Japan) with a rotating rod that accelerated from 0 to 12 rpm. This study was conducted in compliance with the Division for Animal Research Resources, Tokushima University. The experiments and procedures were approved by the Animal Care and Use Committee of Tokushima University (T2024-9) and performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

*Serum liver function test*

To evaluate liver injury, the serum aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels were measured when mice were sacrificed using the Japan Society of Clinical Chemistry standardization matching method. All measurements were performed by Shikoku Chuken, Inc. (Kagawa, Japan).

*Real-time PCR*

Resected liver specimens were homogenized, and total RNA was isolated using an RNeasy Mini Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's protocol. Then, the specimens were used for quantitative analysis of gene expression using quantitative reverse-transcription PCR. cDNA was prepared using a reverse transcription kit (High Capacity cDNA Reverse Transcription Kits ; Applied Biosystems, Foster City, CA, USA). Glyceraldehyde 3-phosphate dehydrogenase (*GAPDH*) (Applied Biosystems) was used as an endogenous control. Liver levels of interleukin-1β (*IL1B*), interleukin-6 (*IL6*), and high mobility group box 1 (*HMGB1*) were assessed using TaqMan gene expression assays (*IL6*, Mm00446190_m1 ; *IL1B*, Mm00434228_m1 ; *HMGB1*, Mm00849805_gH ; Applied Biosystems). TaqMan gene expression assays were conducted in duplicate in 20 mL reactions using TaqMan Array 96-well plates and a real-time PCR System (StepOnePlus ; Applied Biosystems) following the manufacturer's protocol. Standard curves were generated using three-fold serial dilutions of cDNA, and the copy numbers of target genes were calculated in accordance with the standard curves (21).

*Statistical analysis*

Unpaired Mann–Whitney U tests were used to compare variables between the two groups. The survival rate was calculated using the Kaplan–Meier method, and log-rank tests were used for comparisons of differences between two groups. For all statistical analyses, $p<0.05$ was considered significant. All statistical analyses were performed using statistical software (JMP 8.0.1., SAS Campus Drive, Cary, NC, USA).

## RESULTS

*Evaluation of physiobiological status, liver function, and survival rate*

The body weight was not significantly different between the two groups immediately before and 48 hours after hepatectomy (Fig 1a). However, the body weight in the NYT group tended to be higher than that in the control group at 24 hours after hepatectomy ($p=0.09$) (Fig 1a). Grip strength was significantly stronger in the NYT group immediately before and 48 hours after hepatectomy ($p<0.05$) (Fig 1b). Endurance showed no significant difference between the two groups at any point (Fig 1c). Regarding liver function, the serum aspartate aminotransferase level tended to be higher in the NYT group than in the control group at 0 hours ($p=0.07$) (Fig 2). Figure 3 shows the survival rate after hepatectomy with or without NYT. Although the survival time was slightly prolonged in the NYT group, there was no significant difference between the two groups.

*Gene expression in the liver (reverse-transcription PCR)*

Figure 4 shows the mRNA expression levels of *HMGB1*, *IL1B*, *and IL6* at 0, 24 and 48 hours after hepatectomy with or without NYT. *HMGB1* mRNA expression in the liver was significantly suppressed in the NYT group compared with that in the control group ($p<0.05$) at 24 and 48 hours after hepatectomy. There was no significant difference at 0 hours. The mRNA expression of the inflammatory cytokines *IL6* and *IL1B* in the liver showed no significant difference between the two groups at any time.

## DISCUSSION

Herbal medicine, called Kampo, is used in many clinical settings. We previously reported that Daikenchuto showed beneficial effects on microbiome dysbiosis and intestinal injury (21, 22). NYT has been used to promote recovery from various disorders, such as malaise, fatigue, cold sensations, and appetite loss (9-11). NYT was shown to attenuate age-related deficits in muscle performance, self-care motivation, and body temperature (23). NYT was also reported to ameliorate pulmonary emphysema and anxiety/depressive-like behavior in aged model mice (24). Furthermore, NYT inhibits sarcopenia-based physical frailty through its antioxidant effects. In the current study, aged mice also showed improved grip strength and body weight. NYT may affect frailty symptoms after hepatectomy. Regarding its antioxidant effect, liver regeneration was impaired because of oxidative stress caused by the export of excessive $H_2O_2$ after partial hepatectomy (19). High HMGB1 expression leads to oxidative stress and apoptosis (25), and inhibition of HMGB1 restrains ferroptosis and oxidative stress (26). In our study, *HMGB1* expression in the liver was suppressed at 24 and 48 hours after hepatectomy in the NYT group, thus NYT may affect oxidative stress via HMGB1 suppression. In clinical reports, HMGB1 predicted a poor prognosis of hepatocellular carcinoma after curative hepatectomy (27), and patients experiencing postoperative liver failure exhibited elevated intrahepatic and circulating HMGB1 levels, correlating with liver injury markers (28). In a murine model of hepatectomy, inhibition of HMGB1 improved liver function, reduced steatosis, enhanced regeneration, and decreased hepatic cell death (28). Unfortunately, our study could not show that NYT improved the prognosis after hepatectomy in aged mice. However, NYT prolonged prognosis during the 24–48 hours after hepatectomy, which may be partially because of HMGB1 inhibition.

Recently, some reports have shown clinical effects of NYT. Suzuki *et al*. (29) showed that NYT improved activities of daily living and motor/oral function. Furthermore, NYT improved depressive assessments. NYT also improved anorexia and frailty in mild cognitive disorder and Alzheimer's disease patients (30). Furthermore, it improved fatigue after lenvatinib (31) and nab-paclitaxel plus gemcitabine treatment (32). In elderly patients undergoing hepatectomy, preoperative rehabilitation may have promising benefits, such as improving the short-term outcome (33). According to the reports described above, NYT might strengthen the effects of rehabilitation, and we use NYT in the perioperative course of hepatectomy in addition to rehabilitation and nutritional intervention in elderly patients.

The present study has several limitations. First, NYT was administered 1 week before hepatectomy. In other reports using mouse frailty models, 11–13 weeks of NYT administration was performed. Second, only mRNA levels, not protein levels, in the liver were measured. Third, only a naturally aged model was used. Some studies of frailty have used mice with accelerated senescence. Further studies with prolonged NYT administration and other mouse models should be performed.

In conclusion, NYT may affect the postoperative state, including body weight and motor function, in aged model mice. Suppression of HMGB1 might affect postoperative survival.

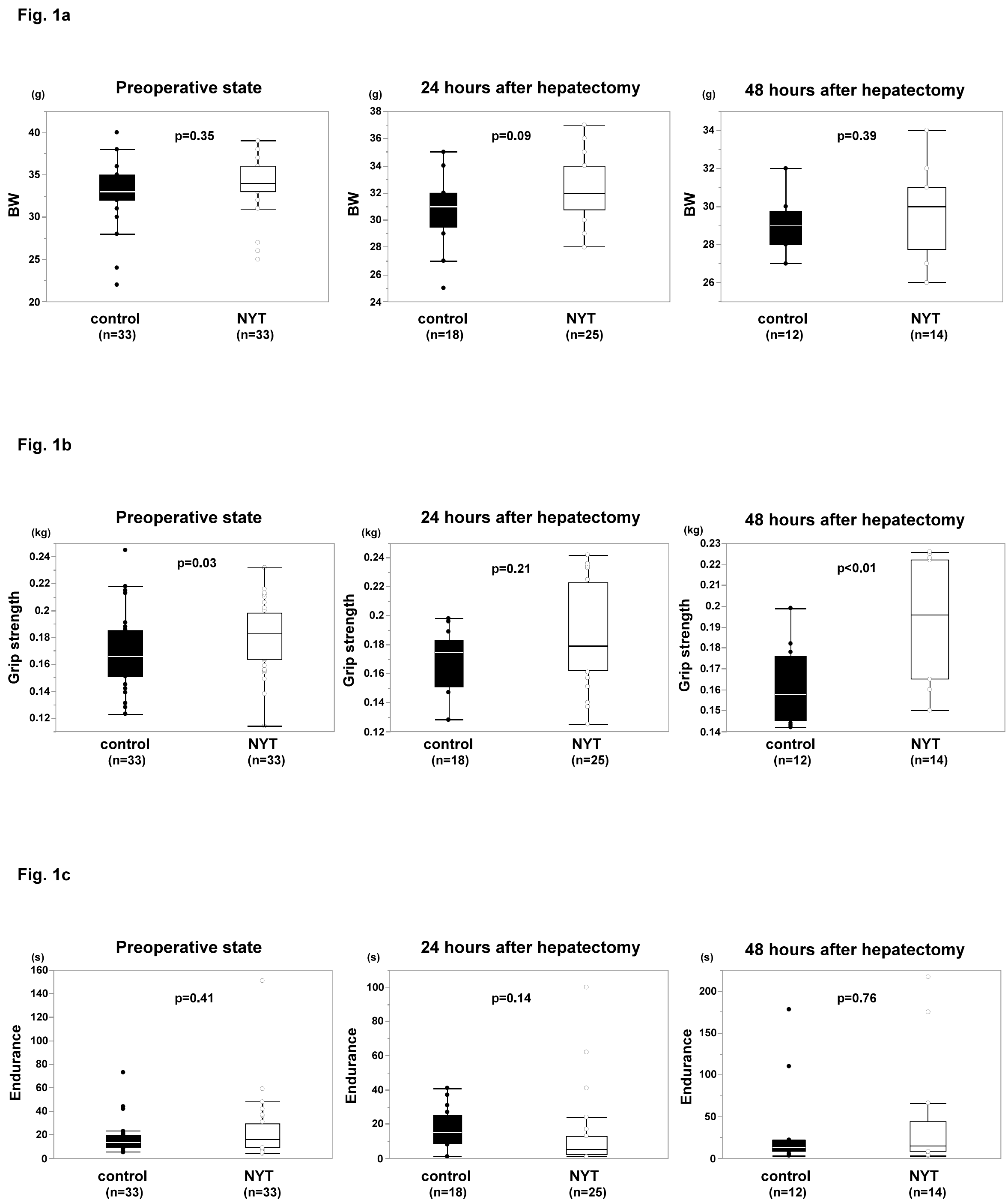


Fig 1. Data for the preoperative state and 24 and 48 hours after hepatectomy. (a) Body weight ; (b) Grip strength ; (c) Endurance using a rotating rod test. Unpaired Mann–Whitney U tests were used. NYT : Ninjin'yoeito

Fig. 2a

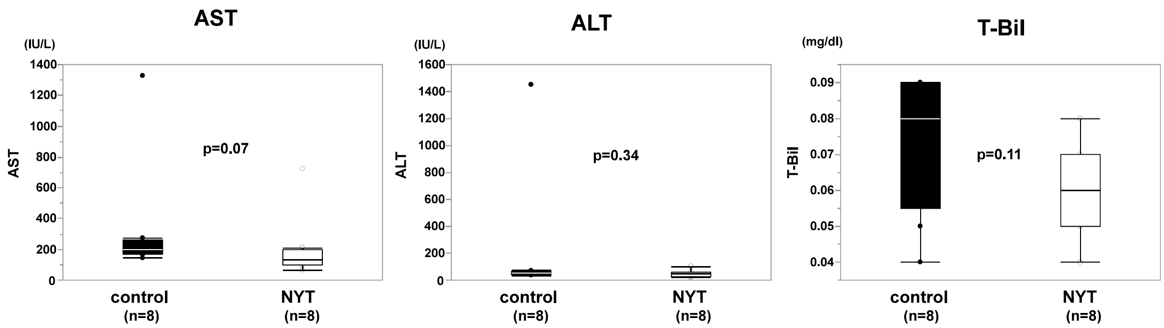


Fig. 2b

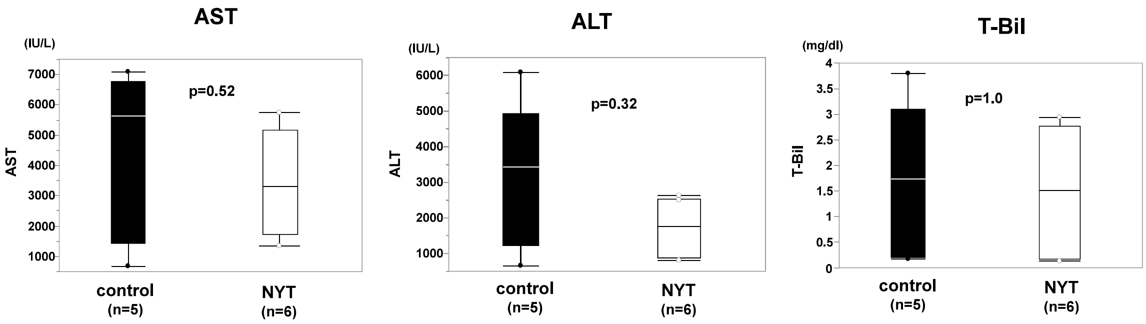


Fig. 2c

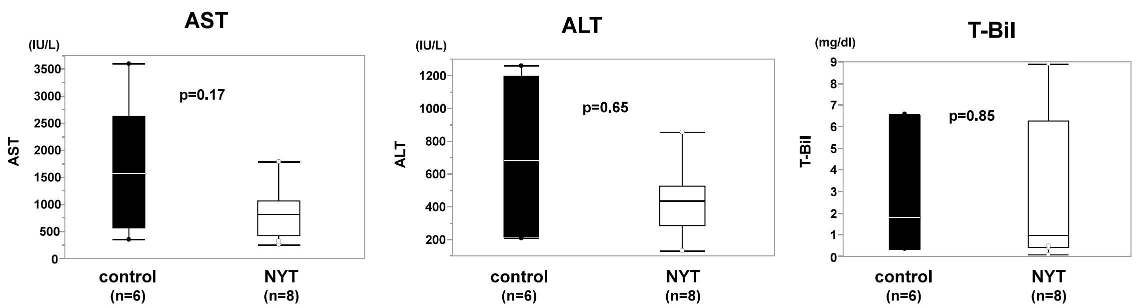


Fig 2. Liver function test. (a) 0 hours after hepatectomy ; (b) 24 hours after hepatectomy ; (c) 48 hours after hepatectomy. Unpaired Mann–Whitney U tests were used. AST : aspartate aminotransferase, ALT : alanine aminotransferase, T-Bil : total bilirubin

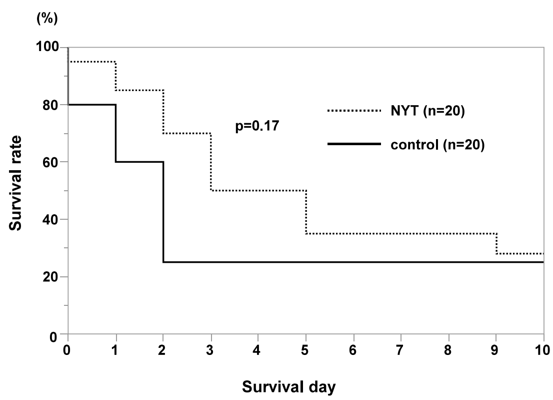


Fig 3. Survival rate calculated by the Kaplan–Meier method. The log-rank test was used to compare the difference between the two groups.

Fig. 4a

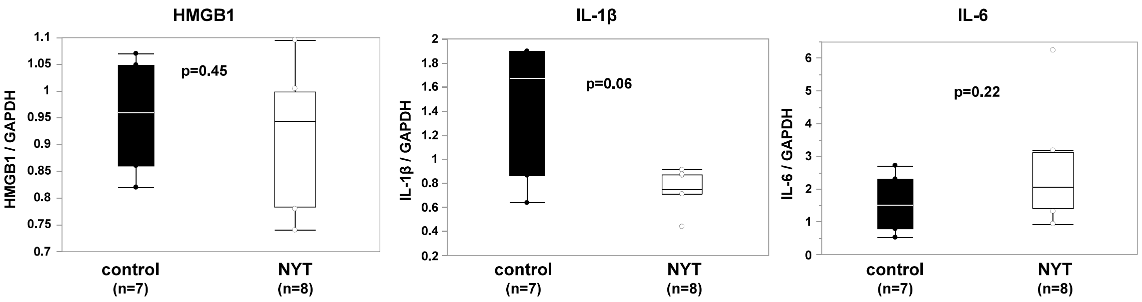


Fig. 4b

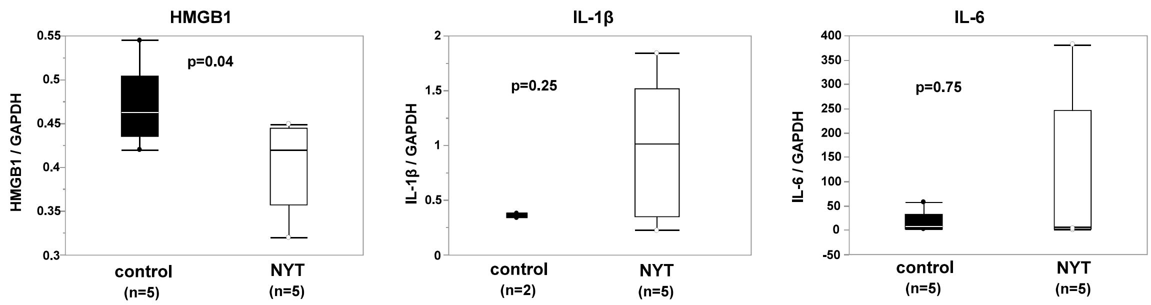


Fig. 4c

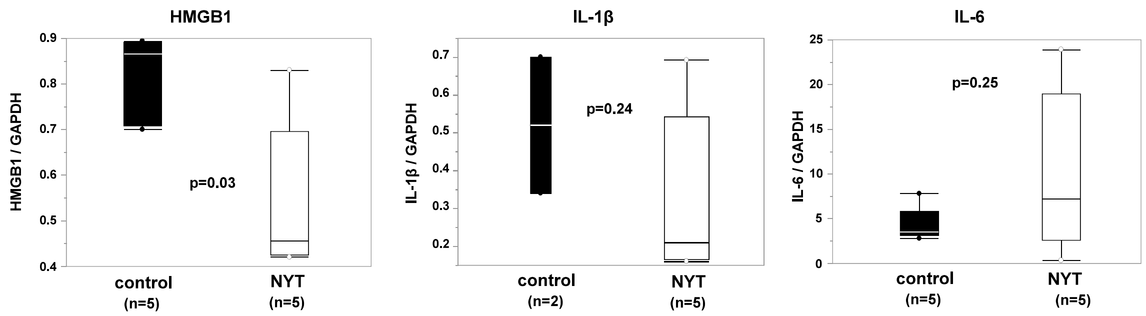


Fig 4. mRNA expression in the liver. (a) 0 hours after hepatectomy ; (b) 24 hours after hepatectomy ; (c) 48 hours after hepatectomy. Unpaired Mann–Whitney U tests were used. GAPDH : glyceraldehyde 3-phosphate dehydrogenase, IL-6 : interleukin-6, IL-1β : interleukin-1β, HMGB1 : high mobility group box 1

## CONFLICT OF INTEREST

The authors have no financial support to disclose

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## AVAILABILITY OF DATA AND MATERIALS

Original data obtained from metagenome/microbiome sequencing of stool samples have been submitted as a supplementary file.

## AUTHOR CONTRIBUTIONS

S.Y., Y.M., and M.S. conceptualized the study. Y.M. and M.S. are responsible for the study supervision and review and editing of the manuscript. S.Y., T.I., Y.S., and H.T. participated in the methodology and data curation. S.Y. participated in writing the original draft and the investigation.

## ETHICS APPROVAL

The experiments and procedures were approved by the Animal Care and Use Committee of Tokushima University (T2024-9) and performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals. The present study was conducted in compliance with the Division for Animal Research Resources, Tokushima University.

## COMPETING INTERESTS

M.S. and Y.M. received a research grant from Tsumura & Co. S.Y. received a reagent (NYT) from Tsumura & Co. Other authors declare no conflict of interest for this manuscript.

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