

1 **Supplementary material for**

2 **Takagi K., et al. Effect of an enhanced recovery after surgery protocol in patients**
3 **undergoing pancreaticoduodenectomy: A randomized controlled trial**

4

5 **Material 1**

6 *The enhanced recovery after surgery protocols.*

7 The preoperative factors were as follows:

8 ▶ Counseling: Given written perioperative information, formal goal-setting, and guidance for
9 refraining from smoking and alcohol;

10 ▶ Mobilization: Assessment and guidance by the rehabilitation team (joint range of motion
11 exercises, muscle strengthening exercises, breathing exercises, pain avoidance behavior
12 guidance, and huffing and cough guidance);

13 ▶ Immunonutrition: Oral supplementation (IMPACT; Nestle Health Science, Japan) for 5
14 days (750 kcal/day) in addition to half of ordinary diet;

15 ▶ No bowel preparation;

16 ▶ Preoperative fasting and carbohydrate loading: Allowed to drink clear liquids up to 2 hours
17 and solids up to 6 hours before surgery and given a carbohydrate drink.

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19 Intraoperative factors were as follows:

20 ▶ No preanesthetic medication;

21 ▶ Standardized anesthesia: Total intravenous anesthesia as per protocol;

22 ▶ Fluid restriction: Anesthesia and goal-directed-therapy (GDT) protocols are shown in

23 Figure 1. The protocol consisted of standardized crystalloid administration (3 mL/kg/hr) and

24 any additional colloid boluses based on the results of hemodynamic monitoring (FloTrac,
25 Edwards Lifesciences, USA). The hemodynamic monitoring was based on the stroke volume
26 index (SVI) (additional colloid bolus given when SVI was less than 30 or monitoring when
27 SVI was greater than 30);

28 ▶ Avoiding hypothermia: Warmed by forced-air warming;

29 ▶ Epidural analgesia: An epidural catheter was inserted between T7 and T10 immediately
30 before surgery and an infusion of bupivacaine 0.2% and fentanyl 2 µg/mL was given and
31 continued until the postoperative period.

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33 Postoperative factors were as follows:

34 ▶ Enteral tube feeding: A feeding tube was replaced intraoperatively at the anal side of the
35 brown anastomosis. Oligomeric formula (PEPTINO; Terumo Corporation, Japan) was started
36 on postoperative day (POD) 1 at a rate of 20 mL/hr. The rate was increased by 10 mL/hr until
37 it reached 50 mL/hr. Feeding was stopped once oral intake was adequate;

38 ▶ Synbiotics: Prebiotics (GFO; Otsuka Pharmaceutical Co., Ltd, Japan) and probiotics
39 (MIYA-BM; Miyarinsan Pharmaceutical Co., Ltd, Japan);

40 ▶ Early oral intake: Oral intake of liquid started on POD 1–2 and solids on POD 3–4;

41 ▶ Early removal of urinary catheter: Removed on POD 2–3;

42 ▶ Early removal of low-risk drains: Removed according to postoperative drain amylase level;

43 ▶ Fluid restriction: Maintained near-zero fluid balance to avoid fluid overload;

44 ▶ Strict glycemic control: Postoperative blood sugar level maintained by diabetologists at 180
45 mg/dL or less by continuous intravenous insulin infusion during the first week and then basal-
46 bolus insulin treatment according to the change in blood sugar level;

47 ▶ Standardized multimodal analgesia: Combined analgesia with epidural analgesia, non-

- 48 steroidal anti-inflammatory drugs, and acetaminophen;
- 49 ▶ Anti-thrombotic prophylaxis: Fractionated low-molecular-weight heparin (CLEXANE;
- 50 Kaken Pharmaceutical Co., Ltd, Japan) for one week;
- 51 ▶ Early scheduled mobilization: Physiotherapy by the rehabilitation team from POD 1 to
- 52 discharge (joint range of motion exercises, muscle strengthening exercises, breathing
- 53 exercises, breathing assistance, and relaxation);
- 54 ▶ Telephone call on the day after discharge.

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56 **Supplementary Fig. 1.** The results of chronologic changes in (a) body weight, (b) fluid
57 volume, (c) urine volume, and (d) drain amylase level. Error bars indicate the standard
58 deviation.

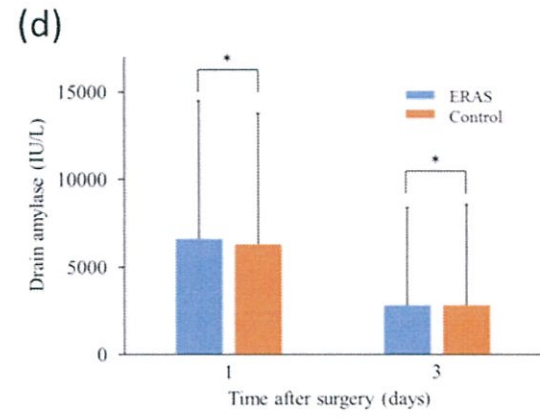
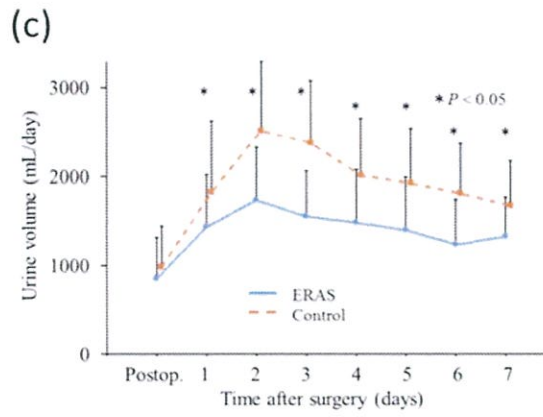
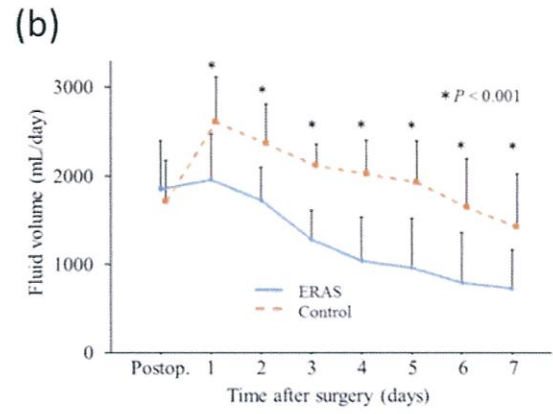
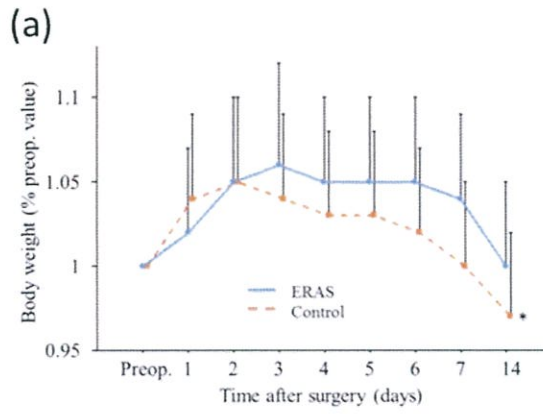
59 (a) Results are expressed as percentage of the preoperative value during the first 14 days after
60 PD. *The body weight on POD 14 was significantly decreased compared to the preoperative
61 value in the control group ($P = 0.004$) but the difference was not significant in the ERAS
62 group.

63 (b) Chronologic changes in mean fluid volume during the first 7 days after PD. *There were
64 significant differences between the groups ($P < 0.001$).

65 (c) Chronologic changes in mean urine volume during the first 7 days after PD. *There were
66 significant differences between the groups ($P < 0.05$).

67 (d) The postoperative drain amylase level during the first 3 days after PD. *The drain
68 amylase level showed no difference between the groups.

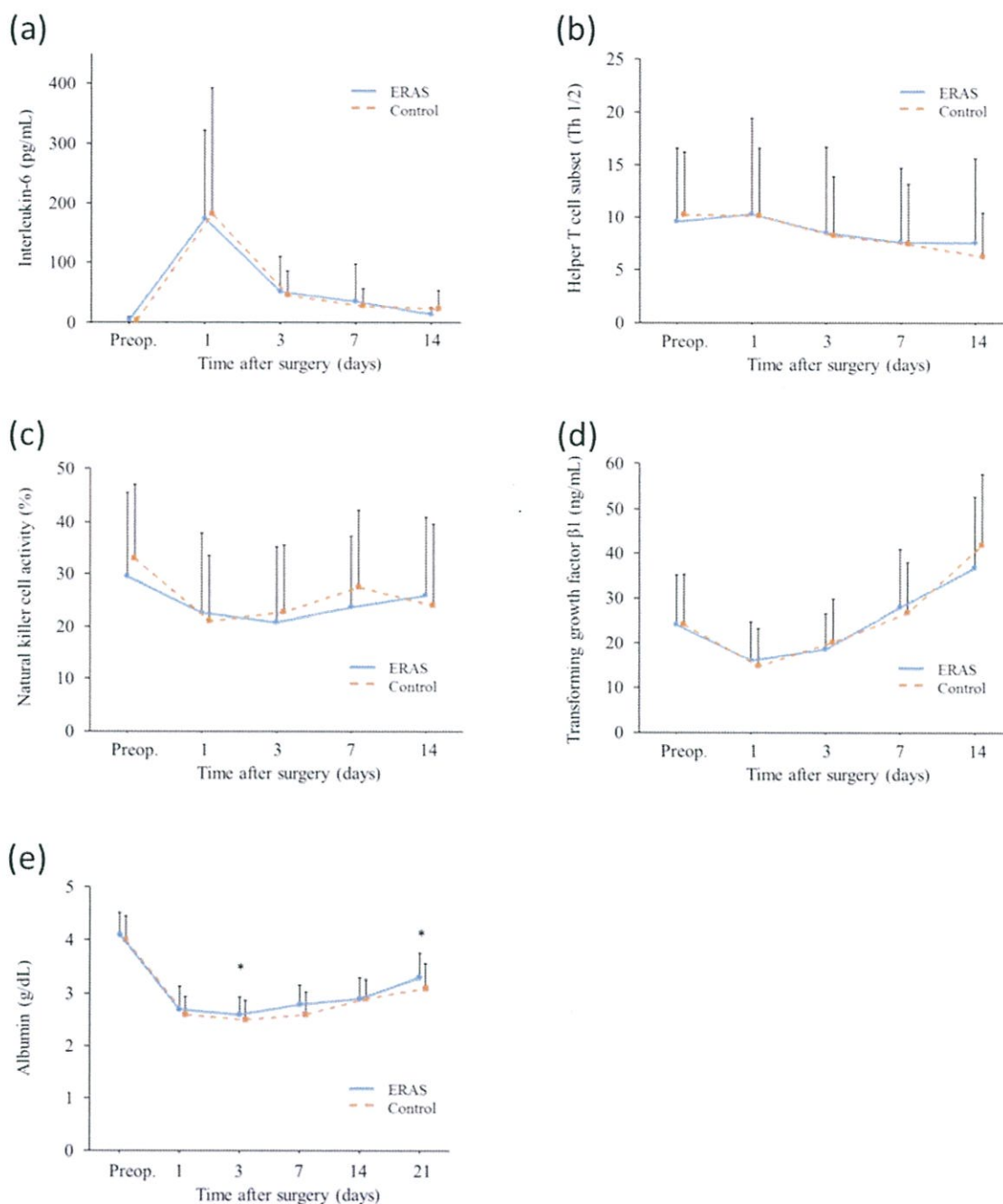
69 ERAS, Enhanced Recovery After Surgery; PD, pancreaticoduodenectomy; POD,
70 postoperative day



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73 **Supplementary Fig. 2.** The results of immune response. The level of (a) interleukin-6, (b)
 74 helper T cell subset (Th 1/2), (c) natural killer cell activity, and (d) transforming growth
 75 factor β 1 (TGF- β 1) were not significantly different between the groups. (e) Albumin levels on
 76 POD 3 and POD 21 were significantly higher in the ERAS group. *There were significant
 77 differences between the groups ($P < 0.05$). Error bars indicate the standard deviation.
 78 POD, postoperative day; ERAS, Enhanced Recovery After Surgery



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