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Injectable Lipid Emulsion and Clinical Outcomes in Patients Exclusively Receiving Parenteral Nutrition in an ICU: A Retro-spective Cohort Study Using a Japanese Medical Claims Data-base

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Abstract: Guidelines for nutritional management of critically ill patients recommend the use of injectable lipid emulsion (ILE) as part of parenteral nutrition (PN). The ILE's ~~use is still limited and its~~ impact on outcomes remains unclear. ~~Investigation of a~~Associations between prescribed ILE and in-hospital mortality, hospital readmission, and hospital length of stay (LOS) in critically ill patients in the intensive care unit~~s~~ (ICU) were investigated. Patients who were ≥ 18 years old, in an ICU from January 2010 through June 2020, receiving mechanical ventilation, and fasting > 7 days, were ~~identified in~~selected from a Japanese medical claims database and divided based on prescribed ILE during days 4 to 7 of ICU admission into 2 groups: no-lipid and with-lipid. Associations between the with-lipid group and in-hospital mortality, hospital readmission, and hospital LOS were evaluated relative to the no-lipid group. Regression analyses and the Cox pro-portional hazards model were used to calculate odds ratios (OR), regression coefficients, and hazard ratios (HR) were adjusted for patient characteristics and parenteral energy and amino acid doses. A total of 20,773 patients were evaluated. Adjusted OR and HR (95% confidence interval) for in-hospital mortality were 0.66 (0.62–0.71) and 0.68 (0.64–0.72), respectively, for the with-lipid group relative to the no-lipid group. No significant differences between the 2 groups were observed for hospital readmission or hospital LOS. The use of ILE for days 4 to 7 in PN prescribed for critically ill patients who were in ~~the~~ an ICU~~s~~ receiving mechanical ventilation and fasting for more than 7 days was associated with a significant reduction of in-hospital mortality.

Keywords: Parenteral nutrition; injectable lipid emulsion; ICU patients; clinical outcomes; real-world data

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1. Introduction

Injectable lipid emulsion (ILE) is the only source of essential fatty acids available to patients who depend on parenteral nutrition (PN) because of an intolerance to oral food intake and enteral nutrition (EN) [1, 2]. Guidelines for nutri-tional management of critically ill patients recommend that ILE be used as part of PN [3, 4]. However, it appears that a certain number of patients receive PN without ILE [5, 6]. Many critically ill patients suffer from malnutrition and a certain number of them depend on PN [7]. Yet when these patients receive PN without ILE, they can develop essential fatty acid deficiency and they may suffer adverse clinical outcomes.

A meta-analysis of studies between 1980 and 1996, before the strategy of permissive underfeeding gained traction, involved critically ill patients and suggested that those receiving PN without ILE had lower complication rates and equivalent mortality rates compared to those receiving PN with ILE [7]. On the other hand, a single-center study published in 2021 of a select group of critically ill surgical patients with hepatic disorder reported the highest mortality rates for those treated with PN without lipid [8]. In addition, ~~a~~ propofol, an anesthetic agent containing lipid as a solvent [9], is often used during mechanical ventilation, but, to our knowledge, there have been no studies of the effects of ILE on clinical outcomes in critically ill patients that have taken propofol into consideration.

The effects of lipid supplementation (taking propofol into account) on the clinical outcomes of critically ill patients receiving PN still need to be clarified. The aim of this study was to investigate the associations between prescribed ILE (including lipid emulsion derived from propofol) and in-hospital mortality, hospital readmission, and hospital lengths of stay (LOS) in patients in ~~the~~an intensive care unit~~s~~ (ICU~~s~~) who were mechanically ventilated and fasting, using a large-scale Japanese national medical claims database ~~in Japan~~.

2. Materials and Methods

2.1. Data source

~~This~~ The medical claims database ~~was a~~used for this retrospective cohort study ~~using a medical claims database~~ was provided by Medical Data Vision (MDV) Co., Ltd. (Tokyo, Japan). At the time that it was used (October 2020), the MDV database covered approximately 33 million patients who had been treated at 400 hospitals, ~~in Japan. These facilities~~ represente~~d~~ing ~~approximately~~ about 23% of the acute care hospitals operating in ~~the country as of October 2020~~Japan. ~~The database contained information including~~Data extracted included ~~dates of~~ hospital admission and dis~~-~~charge dates, ~~patient diagnosis and~~ patient characteristics ~~at~~ upon admission (i.e., age, sex, height, weight, primary diagnosis, comorbidities, activities of daily living, and consciousness levels), medical treatments and drugs prescribed during hospitalization, and clinical outcomes at the time of discharge. T~~Diagnoses were identified using t~~he International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) was used to ascertain diagnoses (Supplementary Table 1). ~~Medical treatments were identified using~~ Japan-specific codes were used to identify medical treatments ~~appearing in medical claims~~ (Supplementary Table 2). The database ~~also enabled extraction of~~ was also used to obtain information about ~~whether~~ the administration to patients of any oral or enteral ~~dietary~~ nutritional intake ~~or EN was received~~ and ~~how many~~all intravenous solution~~s products were prescribed to patients~~. The intravenous product names, compositions, and ~~volum~~numbe~~e~~rs were used to calculate the ~~amounts~~ quantities of parenteral energy, amino acids, ~~and~~ lipid, and carbohydrate prescribed ~~were calculated using the product brand names, compositions, and the number of products prescribed~~.

Table 1. Characteristics of 20,773 patients in ~~the~~ Japanese intensive care units ~~in Japan~~, from January 2010 through June 2020, by groups based on prescribed injectable lipid emulsion during days[1] 4 through 7.

Characteristics	Categories	Patient Groups	
		No-lipid n = 12,312	**With-lipid n = 8,461**
Age, *years*, n (%)	< 60	1,924 (15.6)	1,713 (20.2)
	60–69	2,286 (18.6)	1,763 (20.8)
	70–79	3,577 (29.1)	2,676 (31.6)
	80–89	3,712 (30.1)	2,030 (24.0)
	≥ 90	813 (6.6)	279 (3.3)
Sex, n (%)	Male	7,474 (60.7)	5,678 (67.1)
	Female	4,838 (39.3)	2,783 (32.9)
Body mass index, *kg/m* [2], n (%)	< 16	880 (7.1)	439 (5.2)
	16–18.5	1,866 (15.2)	1,027 (12.1)
	18.5–22.5	4,523 (36.7)	2,955 (34.9)
	22.5–25	2,386 (19.4)	1,895 (22.4)
	≥ 25	2,657 (21.6)	2,145 (25.4)
Beds in admission hospital, n (%)	< 200	323 (2.6)	362 (4.3)
	≥ 200, < 500	7,135 (58.0)	4,741 (56.0)
	≥ 500	4,854 (39.4)	3,358 (39.7)
Admission year, n (%)	2010–2011	409 (3.3)	299 (3.5)
	2012–2013	1,266 (10.3)	850 (10.0)
	2014–2015	2,539 (20.6)	1,770 (20.9)
	2016–2017	3,554 (28.9)	2,485 (29.4)
	2018–2019	3,923 (31.9)	2,642 (31.2)
	2020	621 (5.0)	415 (4.9)
Primary diagnosis[2], n (%)	Sepsis	681 (5.5)	570 (6.7)
	Neoplasm	1,208 (9.8)	1,064 (12.6)
	Diseases of the nervous system	555 (4.5)	215 (2.5)
	Ischemic heart disease	658 (5.3)	693 (8.2)
	Heart failure	800 (6.5)	340 (4.0)
	Cerebrovascular disorders	1664 (13.5)	747 (8.8)
	Other circulatory system diseases	1,664 (13.5)	1,603 (18.9)
	Pneumonia	549 (4.5)	257 (3.0)
	Interstitial respiratory diseases	365 (3.0)	233 (2.8)
	Other respiratory diseases	926 (7.5)	383 (4.5)
	Diseases of the digestive system	1,777 (14.4)	1,324 (15.6)
	Kidney diseases	162 (1.3)	109 (1.3)
	Injury, poisoning, other consequences external causes	551 (5.4)	395 (4.7)
	Other	752 (6.1)	528 (6.2)
Charlson Comorbidity Index, n (%)	0	6687 (54.3)	4,298 (50.8)
	1-2	4,072 (33.1)	2,962 (35.0)
	≥ 3	1,553 (12.6)	1,201 (14.2)
Barthel Index, n (%)	100	2,092 (17.0)	2,131 (25.2)

	65–95	376 (3.1)	312 (3.7)
	45–60	381 (3.1)	268 (3.2)
	25–40	266 (2.2)	149 (1.8)
	5–20	564 (4.6)	342 (4.0)
	0	6,840 (55.6)	4,042 (47.8)
	NA	1,793 (14.6)	1,217 (14.4)
Japan Coma Scale, n (%)	0	5,350 (43.5)	4,680 (55.3)
	1–3	2,123 (17.2)	1,418 (16.8)
	10–30	1,188 (9.6)	710 (8.4)
	100–300	3,650 (29.6)	1,653 (19.5)
	NA	1 (0.0)	0 (0.0)
Surgery[3], n (%)	Cardiovascular	765 (6.2)	1,213 (14.3)
	Gastroenterological	2,383 (19.4)	2,109 (24.9)
	Cerebrovascular	923 (7.5)	437 (5.2)
	Respiratory	29 (0.2)	41 (0.5)
	Orthopedic	32 (0.3)	40 (0.5)
	Urological/Gynecological	63 (0.5)	41 (0.5)
	Multiple surgeries	41 (0.3)	62 (0.7)
	Other	172 (1.4)	194 (2.3)
	No surgery	7,904 (64.2)	4,324 (51.1)
Prescription/treatment[4], n (%)	Catecholamines	8,530 (69.3)	6,519 (77.0)
	Transfusion	5,257 (42.7)	5,129 (60.6)
	Albumin	4,961 (40.3)	5,032 (59.5)
	Renal replacement therapy	2,319 (18.8)	2,225 (26.3)
	Intra-aortic balloon pump	746 (6.1)	920 (10.9)
	Plasmapheresis	62 (0.5)	44 (0.5)
	ECMO	367 (3.0)	531 (6.3)
	Nutritional support team	233 (1.9)	173 (2.0)
	Rehabilitation[5]	5,075 (41.2)	3,838 (45.4)
Parenteral nutrition[6], median (Q1, Q3)	Energy, kcal/kg/d	6.9 (3.8, 11.7)	10.6 (6.8, 15.7)
	~~Carbohydrate, g/kg/d~~	~~1.5 (0.9, 2.5)~~	~~2.0 (1.3, 3.1)~~
	Amino acids, g/kg/d	0.16 (0.00, 0.38)	0.23 (0.04, 0.43)
	Lipid, g/kg/d	0.00 (0.00, 0.01)~~0.0 (0.0, 0.7)~~	0.13 (0.07, 0.22)~~7.5 (3.9, 12.6)~~
	Carbohydrate, g/kg/d	1.5 (0.9, 2.5)	2.0 (1.3, 3.1)
Days without nutrition from day 8[7], median (Q1, Q3)		0.0 (0.0, 1.0)	0.0 (0.0, 0.0)

書式付きの表

Abbreviations: ECMO, extracorporeal membrane oxygenation; Q1, first quartile; Q3, third quartile.

[1] The day of admission to the ICU was considered day 1~~[1] Day 1 regarded as day of intensive care unit admission~~.

[2] Diagnoses ~~identified using~~based on International Statistical Classification of Diseases and Related Health Problems, 10th revision.

[3] Between days of hospital ~~admission and day of~~and intensive care unit admissions, ~~based on~~identified using Japan-specific codes.

[4] ~~During~~ Between days 1 ~~to~~ and 7 of intensive care unit admission.

[5] Feeding therapy and/or rehabilitation for cardiac ma~~i~~crovascular, cerebrovascular, disuse syndrome, locomotor, and/or respiratory diseases.

[6] Medians of mean prescribed daily doses during days 1 to 7 of intensive care unit admission.

[7] Days without nutrition (oral intake, enteral nutrition, or parenteral amino acids/lipid) from day 8 to day of discharge or in-hospital death.

Table 2. Clinical outcomes in 20,773 patients in ~~the~~ Japanese intensive care units ~~in Japan~~, from January 2010 through June 2020, by groups based on injectable lipid emulsion during days[1] 4 through 7.

	Patient Group		Odds ratio/regression coefficient (95% CI)[2]		
	No-lipid n = 12,312	With-lipid n = 8,461	Unadjusted	Model 1[3]	Model 2[4]
In-hospital mortality, n (%)	5,863 (47.6)	2,958 (35.0)	0.59 (0.56–0.63)	0.62 (0.58–0.67)	0.66 (0.62–0.71)
Hospital readmission[5,6], n (%)	270 (4.2)	241 (4.4)	1.03 (0.85–1.25)	0.96 (0.78–1.18)	0.94 (0.76–1.15)
Hospital LOS[5], median (Q1,Q3)	45 (29, 71)	48 (31, 73)	1.96 (-0.43–4.35)	0.58 (-1.88–3.04)	0.78 (-1.69–3.25)

Abbreviations: CI, confidence interval; LOS, length of stay; Q1, first quartile; Q3, third quartile.
[1] The day of admission to the ICU was considered day 1~~Day 1 regarded as day of intensive care unit admission~~.
[2] Odds ratios and regression coefficients calculated for with-lipid group with no-lipid group used as reference.
[3] Adjustments made for age, sex, BMI, beds in admission hospital, primary diagnosis, admission year, Charlson Comorbidity Index, Barthel Index, Japan Coma Scale, surgery, catecholamines, transfusion, albumin, renal replacement therapy, intra-aortic balloon pump, extracorporeal membrane oxygenation, nutritional support team, rehabilitation, and mean prescribed daily doses of energy and amino acid on days 1 through 7.
[4] Adjustments made for all of the variables used in Model 1 as well as days without nutrition from day 8 to day of discharge or in-hospital death.
[5] Surviving discharged patients~~,~~ n = 6,449 in the no-lipid group, n = 5,503 in the with-lipid group.
[6] Patients who were readmitted within 30 days of discharge to ~~same~~ the hospital of~~as initial~~ original admission.

2.2. Patient population

~~This study included P~~patients were included in this study who were aged 18 years or older, were ~~who were~~ admitted to an ICU between January 2010 and June 2020, ~~remained in that~~were in ~~the~~an ICU~~s~~ for 4 days or longer, received mechanical ventilation on ~~the first, second, and/or third day~~any of the first 3 days of ICU admission, survived and remained ~~in the hospital~~hospitalized longer than 7 days, and were fasting (i.e., receiving ~~neither~~ no oral ~~food intake nor EN~~or enteral nutrition) for longer than 7 days. For this study, ~~day 1 was regarded as~~ the day of admission to ~~the~~an ICU ~~admission~~was considered to be day 1. Patients were excluded from the study ~~whose~~ who had missing data or suspected input data errors for height, weight, or prescribed parenteral energy amounts. Input errors were defined as ~~data were missing or suspected to be the result of input errors (i.e.,~~ height < 100 cm or ≥ 200 cm, weight < 10 kg or ≥ 200 kg, and/or 0 kcal of prescribed energy ~~prescribed~~ between~~of 0 kcal during~~ days 1 and~~to~~ 7~~)~~.

2.3. Patient group

~~In order to investigate~~To explore the association between ILE and clinical outcomes, patients were divided into 2 groups: the no-lipid group, who were not prescribed lipid during days 4 through 7, and the with-lipid group, who were prescribed lipid during days

4 through 7. As it is recommended that the dose from artificial nutrition be limited during the initial 3 days of ICU admission [3], the presence of prescription days 4 through 7 in the ICU were used in this study. In Japan, only soybean-oil containing injectable lipid (SO ILE) is available as the lipid in PN. Propofol is dissolved in soybean oil or both soybean oil and medium chain fatty acids.

2.4. Endpoints

The primary endpoint was in-hospital mortality, and the secondary endpoints were hospital readmission and ~~hospital~~ LOS. Only ~~surviving discharged patients~~ those patients who were discharged and had survived were evaluated for secondary endpoints. The definition of h~~H~~ospital readmission was ~~defined as being admitted~~reentering the original hospital within 30 days of being discharge~~d to the same hospital as the initial admission~~.

2.5. Data extraction

Data were extracted or calculated from the database and categorized as follows: age (< 60, 60 to 69, 70 to 79, 80 to 89, or ≥ 90 years), sex, body mass index (BMI) (< 16, ≥ 16 to < 18.5, ≥ 18.5 to < 22.5, ≥ 22.5 to < 25, or ≥ 25; according to the WHO classification [11]), ~~number of beds of~~ admission hospital bed numbers (< 200, ≥ 200 to < 500, or ≥ 500), admission year (2010 to 2011, 2012 to 2013, 2014 to 2015, 2016 to 2017, 2018 to 2019, or 2020), primary admission diagnosis (from 10 disease categories ~~based on~~according to ICD-10 codes (Supplementary Table 1)), severity of comorbidities (0, 1 to 2, or ≥ 3; according to Charlson Comorbidity Index [CCI] score in ~~conjunction~~ combination with the algorithm ~~developed~~ established by Quan et al [12]), activities of daily living (0, 5 to 20, 25 to 40, 45 to 60, 65 to 95, or 100; assessed at hospital admission after being critically ill, using Barthel Index [BI] [13]), level of consciousness according to the Japan Coma Scale (JCS) [14]~~level~~ (i.e., JCS0 [alert]; JCS1, 1-digit code [not fully alert, but awake without any stimuli]; JCS2, 2-digit code [arousable with stimulation]; or JCS3, 3-digit code [unarousable]~~; according to Japan Coma Scale (JCS) [14]~~), and surgeries ~~undergone~~ undertaken between days of ~~hospital admission and day of~~hospital and ICU admission~~s~~, based on Japan-specific codes (Supplementary Table 2).

Data extracted also included drugs prescribed or medical treatments received ~~during~~ from day~~s~~ 1 ~~through~~ to day 7 of hospital admission: catecholamines (dobutamine, dopamine, epinephrine, and norepinephrine), transfusions (fresh frozen plasma, platelets, and/or red blood cells), albumin, renal replacement therapy, intra-aortic balloon pump, plasmapheresis, extracorporeal membrane oxygenation (ECMO), ~~intervention by~~ nutritional support team (NST) intervention, rehabilitation (for cardiac macrovascular disease, cerebrovascular disease, disuse syndrome, locomotor disease, and/or respiratory disease), and/or feeding therapy.

For the calculations of d~~D~~aily prescribed parenteral doses of energy, amino acids, ~~and~~ lipid, and~~,~~ carbohydrate the ~~were calculated using the~~ extracted ~~data of~~information about number of ~~prescribed number of~~ parenteral nutrition products ~~and their compositions~~that were prescribed were used. ~~For the determinations of daily~~Daily prescribed parenteral doses of lipid included ~~,~~ propofol~~–~~ when prescribed~~was also included~~. ~~For the determinations of daily~~Daily prescribed parenteral doses of energy included ~~,~~ carbohydrate solutions that were used for ~~drug preparation,~~ maintenance hydration, glucose-containing extracellular fluid expansion, drug preparation, and propofol administration ~~were also included~~. Also, the days without nutrition (oral intake, EN, or parenteral amino acids/lipid) from day 8 to day of discharge or in-hospital death was calculated.

Mean prescribed doses of energy (kcal/kg/day), amino acids (g/kg/day), ~~and~~ lipid (g/day)~~,~~ and carbohydrate (g/kg/day) during days 1 through 7 were calculated. Median prescribed daily doses of energy, amino acids, ~~and~~ lipid, and carbohydrate by group were calculated and graphed to demonstrate trends over time. The ideal body weight (= 22 × [height, m^2]) was used w~~W~~hen ~~the~~ dose~~s~~ per body weight was ~~calculated~~determined, ~~the~~

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~~ideal body weight (= 22 × [height, m²]) was used~~in order~~,~~ to avoid underestimating target doses of nutrition that may be caused by the tendency toward low body weight relative to height in Japanese patients.

2.6. Statistical analysis

Statistical analysis was conducted by an independent third party (A2 Healthcare Corporation, Tokyo, Japan) to exclude bias and ensure transparency. Summary statistics of categorical variables were ~~expressed as~~ shown ~~as~~ using frequencies and percentages, and those of continuous variables were ~~expressed as~~shown using medians, first quartiles (Q1), and third quartiles (Q3). ~~Patients whose~~When there was missing data for BI or JCS, ~~could not be determined because of missing data had~~ those characteristics ~~categorized~~ were listed as 'not available' (NA). The multivariate logistic regression analysis, the univariate regression analysis, and the analyses with the Cox proportional hazard model were performed with adjustment for the factors as follows, from clinical viewpoints: age; sex; BMI; ~~beds in~~ admission hospital beds; admission years; primary diagnosis; Charlson Comorbidity Index; Barthel Index; JCS; surgery type; prescription/treatment of catecholamine, transfusion, albumin, renal replacement therapy, intra-aortic balloon pump, plasmapheresis, ECMO, NST intervention, and rehabilitation; mean prescribed doses of energy from day 1 to 7; mean doses of amino acids from day 1 to 7.

Associations between the 2 groups and in-hospital mortality or hospital readmission were analyzed with univariate logistic regression. Associations were also analyzed with multivariate logistic regression analysis, ~~adjusting~~ with adjustments for the factors described above. Odds ratios (OR), adjusted odds ratios (AOR), and 95% confidence intervals (CI) were calculated for the with-lipid group, with the no-lipid group used as the reference.

Associations between the 2 groups and hospital LOS were analyzed with univariate regression. Associations were also analyzed with multiple regression, adjusting for the 2 lipid groups and the factors described above. Regression coefficients before and after adjustments and 95% CI were calculated for the with-lipid group, with the no-lipid group used as the reference.

Kaplan-Meier survival curves were generated for in-hospital mortality, and the log-rank test was performed to investigate the differences between the 2 groups. Furthermore, the Cox proportional hazard model was used to calculate adjusted hazard ratios (AHR) and 95% CI for the with-lipid group, with the no-lipid group as the reference. The hazard ratios were adjusted for the factors above. Patients discharged alive were censored on the day of discharge, and inpatients surviving for 90 days or longer were censored on Day 90.

A sensitivity analysis was performed after dividing the with-lipid group into 3 lipid subgroups, based on whether ILE or propofol was prescribed during days 4 to 7, as follows: ILE-only subgroup, ILE+ propofol subgroup, and propofol-only subgroup. The no-lipid group was used as the reference in the analysis. Associations between the 4 subgroups including no-lipid group and in-hospital mortality or hospital readmission were analyzed with univariate logistic regression. Also, these associations were analyzed with multivariate logistic regression, adjusting for the 4 subgroups and the factors described above. OR, AOR, and 95% CI were calculated for the 3 subgroups, with the no-lipid group used as the reference. Associations between the 4 subgroups including no-lipid group and hospital LOS was analyzed with univariate regression. Also, these associations were analyzed with multiple regression, adjusting for the 4 subgroups and the factors described above. Regression coefficients before and after adjustment and 95% CI were calculated for the 3 with-lipid subgroups, with the no-lipid group used as the reference.

All of AORs, adjusted regression coefficients, and AHRs above were calculated using 2 models, Model 1 and Model 2. Model 1 did not include the days without nutrition from day 8 to discharge or in-hospital death as an adjustment factor, but Model 2 included it. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc.; Cary, NC, USA). A two-sided significance level of 5% was used.

3. Results

3.1. Patient characteristics

Of the 23,406 patients in ~~the~~ an ICU ~~who received~~receiving mechanical ventilation and ~~were~~ fasting long-term (> 7 days), 20,773 met the inclusion criteria (Figure 1). Of those, 12,312 (59.3%) patients were in the no-lipid group and 8,461 (40.7%) patients were in the with-lipid group (Table 1). A total of 4,525 (36.8%) patients in the no-lipid group and 2,309 (27.3%) patients in the with-lipid group were 80 years or older, while 2,746 (22.3%) patients in the no-lipid group and 1,466 (17.3%) patients in the with-lipid group had BMI ~~less than~~at or below 18.5. The most ~~common~~ prevalent primary diagnosis in the no-lipid group was disease of digestive system in 1,777 (14.8%) patients, followed by cerebrovascular disorders in 1,664 (13.5%) patients, and other circulatory system diseases in 1,664 (13.5%) patients. The most ~~common~~ prevalent primary diagnosis in the with-lipid group was other circulatory system diseases in 1,603 (18.9%) patients, followed by disease of digestive system in 1,324 (15.6%) patients, and neoplasm in 1,064 (12.6%) patients.

The median (Q1, Q3) of the mean prescribed daily energy doses during days 1 through 7 ~~was~~ 6.9 (3.8, 11.7) kcal/kg in the no-lipid group and 10.6 (6.8, 15.7) kcal/kg in the with-lipid group (Table 1). The median (Q1, Q3) of the mean prescribed daily lipid doses during days 1 through 7 was 0.00 (0.00, 0.017) g/kg~~day~~ in the no-lipid group and ~~7~~0.~~5~~13 (~~3.9~~0.07, ~~12.6~~0.22) g/kg~~day~~ in the with-lipid group. The median (Q1, Q3) of the mean prescribed daily carbohydrate doses during days 1 through 7 was 1.5 (0.9, 2.5) g/kg in the no-lipid group and 2.0 (1.3, 3.1) g/kg in the with-lipid group. The medians of the prescribed ~~parenteral doses of~~ energy, amino acid~~s~~, ~~and~~ lipid, and carbohydrate doses for each group were calculated for days 1 through 7, to illustrate the changes in the prescribed doses over time (Figure 2). On day 7, the median (Q1, Q3) prescribed energy dose was 8.8 (3.7, 16.7) kcal/kg/day for the no-lipid group and 14.6 (7.4, 21.4) kcal/kg/day for the with-lipid group.

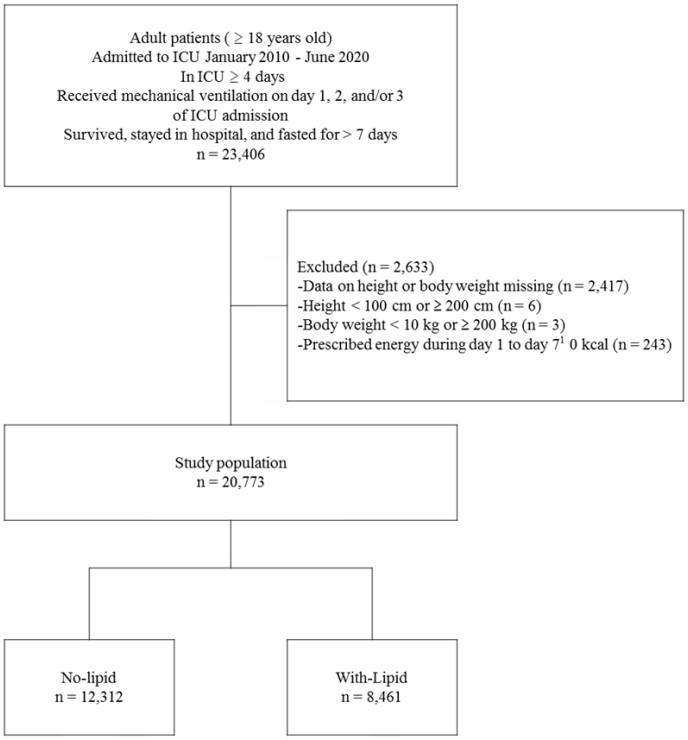
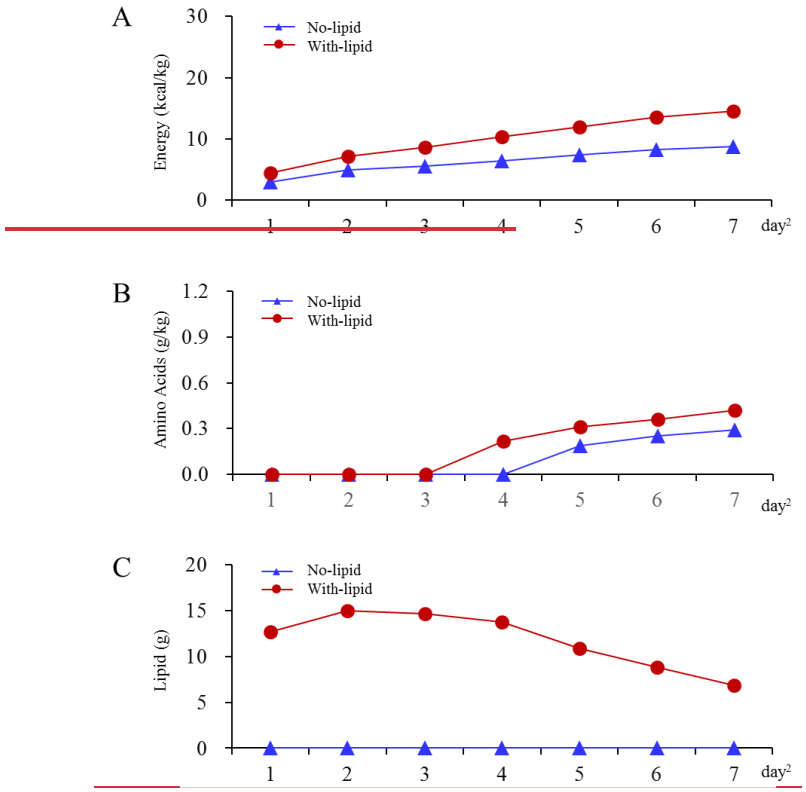


Figure 1. Study and patient disposition flowchart. [1] The day of admission to the ICU was considered day 1. ~~[1] Day 1 regarded as the day of intensive care unit (ICU) admission.~~



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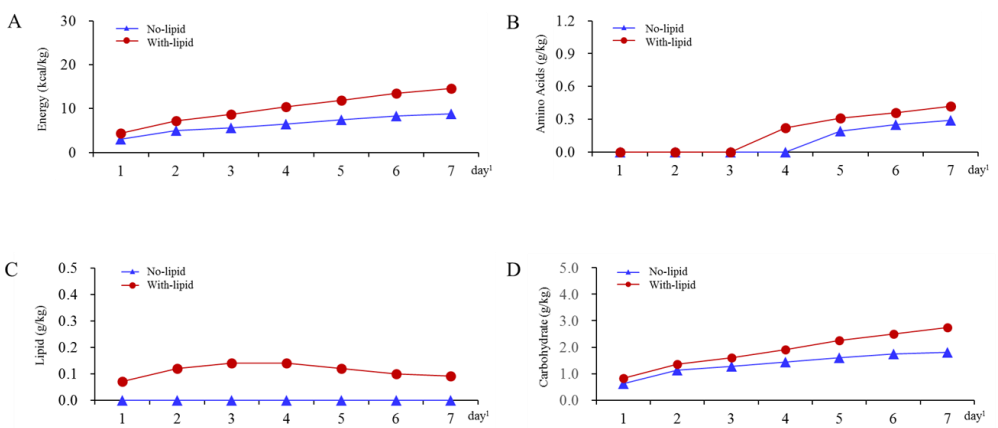

Figure 2. Median prescribed daily doses of parenteral nutrition on days 1 through 7 of ICU admission in no-lipid and with-lipid groups, among 20,773 patients in Japan, from January 2010 through June 2020. The changes in the prescribed doses over time in ~~the~~ an ICU are shown. The medians of the prescribed daily doses of energy and amino acids increased slightly for both groups between day 1 and day 7, whereas the medians of the doses of lipid decreased after day 2 in the with-lipid group. (A) The change in prescribed energy dose over time. (B) The change in prescribed amino acid dose over time. (C) The change in prescribed lipid dose over time. (D) The change in prescribed carbohydrate dose over time. ~~1~~ ~~Day 1 regarded as the day~~The day of admission to the ~~of~~ ICU ~~admission~~was considered day 1.

3.2. Endpoints

In-hospital mortality occurred in 5,863 (47.6%) patients in the no-lipid group, but in only 2,958 (35.0%) patients in the with-lipid group (Table 2). The AORs (95% CI) of in-hospital mortality for the with-lipid group relative to the no-lipid group were 0.62 (0.58–0.67) (Model 1) and 0.66 (0.62–0.71) (Model 2). Kaplan-Meier curves were generated and the survival rate for the with-lipid group was significantly higher than for the no-lipid group ($p < 0.001$) (Figure 3). The AHRs (95% CI) of in-hospital mortality for the with-lipid group relative to the no-lipid group were 0.68 (0.64–0.71) (Model 1) and 0.70 (0.67–0.73) (Model 2). No significant differences were found in the AORs for hospital readmission or the adjusted regression coefficients for hospital LOS between the 2 groups (Table 2).

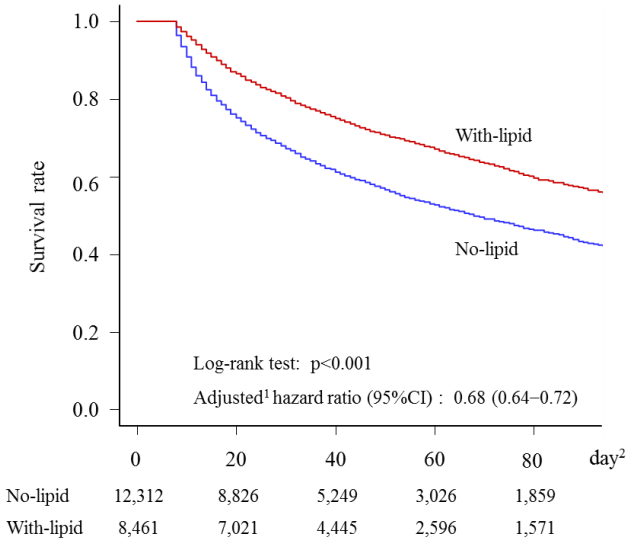

Figure 3. Kaplan-Meier survival curves and adjusted[1] hazard ratios of in-hospital mortality (days[2] 1 through 90) in no-lipid and with-lipid groups, among 20,773 patients in Japan, from January 2010 through June 2020. The survival rate for the with-lipid group was significantly higher than for the no-lipid group ($p < 0.001$). The adjusted hazard ratio of in-hospital mortality for the with-lipid group compared to the no-lipid group was 0.68. [1] ~~Adjustments made~~Hazard ratios were adjusted for age, sex, BMI, ~~beds in~~ admission hospital beds, primary diagnosis, year of admission~~-year~~, Charlson Comorbidity Index, Barthel Index, Japan Coma Scale, surgery, catecholamines, transfusion, albumin, renal replacement therapy, intra-aortic balloon pump, extracorporeal membrane oxygenation, nutritional support team intervention, rehabilitation, mean prescribed daily energy and amino acid doses ~~during~~ from days ~~1 through~~ to day 7, and days without nutrition from day 8 to day of discharge or in-hospital death. [2] The day of admission to the ICU was considered day 1. ~~[2] Day 1 regarded as the day of intensive care unit admission.~~

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3.3. *Sensitivity analysis*

Among the patients in the with-lipid group, there were 1,073 (12.7%) patients in the ILE-only subgroup, 541 (6.4%) patients in the ILE+ propofol subgroup, and 6,847 (80.9%) patients in the propofol-only subgroup (Table 3). ~~The~~ For Model 1, the AORs (95% CI) of in-hospital mortality relative to the no-lipid group were 0.82 (0.71–0.96) for the ILE-only group, 0.68 (0.55–0.84) for the ILE+propofol group, and 0.59 (0.55–0.64) for the propofol-only group~~p (Model 1)~~. ~~Those~~ For Model 2, they were 0.87 (0.75–1.01) for the ILE-only group, 0.71 (0.57–0.87) for the ILE+propofol group, and 0.63 (0.58–0.68) for the propofol-only group ~~(Model 2)~~. No significant differences were found in the AORs of hospital readmission or the adjusted regression coefficients of hospital LOS between each of the 3 with-lipid subgroups and the no-lipid group.

Table 3. Clinical outcomes in 20,773 patients in the intensive care units in Japan, from January 2010 through June 2020, by subgroups based on whether ILE or propofol was prescribed on days[1] 4 through 7.

	Patient Subgroups		
	ILE-only n = 1,073	ILE+ propofol n = 541	Propofol-only n = 6,847
	Unadjusted odds ratio/regression coefficient (95% CI)[2]		
In-hospital mortality	0.74 (0.64–0.85)	0.63 (0.52–0.77)	0.57 (0.54–0.61)
Hospital readmission[3,4]	1.08 (0.71–1.65)	1.01 (0.56–1.82)	1.02 (0.84–1.26)
Hospital LOS[5], median	2.34 (-3.02–7.70)	5.24 (-2.08–12.55)	1.67 (-0.86–4.19)
	Model 1[5] odds ratio/regression coefficient (95% CI)[2]		
In-hospital mortality	0.82 (0.71–0.96)	0.68 (0.55–0.84)	0.59 (0.55–0.64)
Hospital readmission[3,4]	1.01 (0.65–1.56)	0.93 (0.50–1.71)	0.96 (0.77–1.19)
Hospital LOS[3]	2.39 (-2.91–7.70)	2.97 (-4.27–10.21)	0.10 (-2.52–2.71)
	Model 2[6] odds ratio/regression coefficient (95% CI)[2]		
In-hospital mortality	0.87 (0.75–1.01)	0.71 (0.57–0.87)	0.63 (0.58–0.68)
Hospital readmission[3,4]	0.98 (0.64–1.52)	0.92 (0.50–1.70)	0.93 (0.75–1.16)
Hospital LOS[3]	2.65 (-2.67–7.96)	3.18 (-4.07–10.42)	0.29 (-2.33–2.91)

Abbreviations: ILE, injectable lipid emulsion; CI, confidence interval; LOS, length of stay.

[1] The day of admission to the ICU was considered day 1.

~~[1] Day 1 regarded as day of intensive care unit admission.~~

[2] Odds ratios and regression coefficients calculated for with-lipid subgroups, with the no-lipid group (n = 12,312) used as reference.

[3] Surviving discharged patients; n = 6,449 in the no-lipid group, n = 650 in the ILE-only group, n = 346 in the ILE+propofol group, and n = 4,507 in the propofol-only group.

[4] ~~Patients who were admitted within 30 days of discharge to same hospital as initial admission.~~ Patients who were readmitted within 30 days of discharge to the hospital of original admission.

[5] ~~Adjustments made~~ Adjusted for age, sex, BMI, ~~beds in~~ admission hospital beds, primary diagnosis, year of admission ~~year~~, Charlson Comorbidity Index, Barthel Index, Japan Coma Scale, surgery, catecholamines, transfusion, albumin, renal replacement therapy, intra-aortic balloon pump, extracorporeal membrane oxygenation, nutritional support team intervention, rehabilitation, and mean prescribed daily doses energy and amino acid from day 1 to day 7 ~~on days 1 through 7~~.

[6] ~~Adjustments made~~ Adjusted for all of the variables used in Model 1, as well as days without nutrition from day 8 to day of discharge or in-hospital death.

4. Discussion

We investigated the effects of ILE prescribed during days 4 through 7 of ICU admissions on the clinical outcomes of patients who were mechanically ventilated and fasting for more than 7 days. We found a significant inverse association between prescribed ILE and in-hospital mortality. No significant differences were observed for hospital readmission or hospital LOS. Our study involving more than 20,000 patients provides strong evidence that ILE prescribed in the ~~early~~ period soon after admission to ~~the~~an ICU ~~admission~~ may reduce in-hospital mortality in critically ill patients.

An older meta-analysis that included 2,211 critically ill patients receiving PN reported that patients without ILE had lower complication rates and equivalent mortality rates compared to those who received PN with ILE [6]. However, that report only included studies conducted before 1996, and many of the patients received high energy doses of 35 kcal/kg/day or more. It is possible that the benefits of adding ILE may have been masked by the effects of overfeeding, which can adversely impact prognosis in critically ill patients [15]. On the other hand, our study of 20,773 patients involved a larger sample size and lower prescribed energy doses (8.8 kcal/kg/day in the no-lipid group and

14.6 kcal/kg/day in the with-lipid group). It may be that the inclusion of ILE in PN for patients in ICU exerts a favorable impact~~s~~ on mortality only when overfeeding is avoided.

Another reason for the different conclusions between two studies might be complex differences in control groups or patient characteristics. Many of the control group, compared to the study group (PN with ILE group) in the trials reviewed for the meta-analysis was 5% dextrose solution group, EN group, or oral feeding group, and the conclusion of the meta-analysis might not come from the influence of ILE alone. Almost all study patients for the trials reviewed for the meta-analysis were postoperative patients not limited to ICU patients. In addition, many patients in such trials received more lipids and amino acids than the study patients in our current study did.

In this study, the prescribed amino acid dose was 0.16 g/kg/d in the No-lipid group and 0.23 g/kg/d in the With-lipid group, both of which were lower than that in the guidelines [3, 4] and study results in other countries except Japan [16, 17]. But the low prescribed dose of amino acids shown in this study was similar to other previous surveys of clinical nutrition management in Japanese ICUs [5, 18]. In Japan, prescribed energy is tended to be reduced as increasing the awareness of permissive underfeeding; while, the awareness of the importance of amino acids is low and amino acid solutions are seldom added to the 2-in-1 products widely used in Japan, which seems to lead the small prescribed amino acid dose [5].

A possible reason for the favorable impact of ILE on hospital survival is ~~their~~ its protein-sparing effect. One systematic review of critically ill patients receiving PN reported that free fatty acid concentrations in the blood were maintained, nitrogen balance was improved, and, most importantly, proteins were spared in groups receiving PN with ILE [1]. A study of critically ill patients suggested that another benefit of ILE as part of PN was the suppression of endogenous glucose production [1~~6~~9]. When endogenous glucose is produced, amino acids are consumed [~~17~~20]. The findings of these studies, along with our results, suggest that the protein-sparing effect of ILE may be at least one of the explanations for the improvements in survival of critically ill patients who receive ILE supplementation. In addition, an excessive carbohydrate dosing can be avoided by the use of ILE, which may result in an avoidance of hyperglycemia [21]. And the avoidance of hyperglycemia may lead to the improvement of clinical outcomes. However, in this study, median (Q1, Q3) of the carbohydrate dose for the No-Lipid group of 1.5 (0.9, 2.5) g/kg/d was lower than that for the With-Lipid group, 2.0 (1.3, 3.1) g/kg/d; therefore, it is unlikely that the No-Lipid group had more patients with hyperglycemia. As the database used in this study does not include the data of plasma glucose level, we cannot discuss the issue well at this moment. In the future, effects of ILE on the plasma glucose control should be investigated.

In Japan, whereas ~~the use of~~ ILE use for critically ill patients has been limited, propofol ~~is~~ has been used more often, particularly for patients who are mechanically ventilated [5, 9]. In our study, 7,388 (35.6%) patients were prescribed propofol (which contains ILE as a solvent) during days 4 through 7 of their ICU admission. Because of this, we opted to include in our study a sensitivity analysis in which clinical outcomes were compared between the 3 with-lipid subgroups (ILE-only, ILE+propofol, and propofol-only) and the no-lipid subgroup.

Both prescribed energy and amino acid doses tended to be higher in the ILE-only group and the ILE+propofol group than in the propofol-only group (Supplementary Table 3). This result might be related to the comparatively high awareness of nutritional management in the physicians who prescribe ILE. As the prescribed energy and amino acid doses differed between subgroups, a multivariate analysis was performed where adjustment was made for not only patient characteristics but also parenteral energy and amino acid doses for the statistical analysis of subgroups. Relative to the No-lipid group, the AOR of in-hospital mortality for each of the 3 subgroups ~~tended to~~ was significantly lower, with the exception that this difference was not quite statistically significant for the ILE-only group when the OR was additionally adjusted for days without nutrition from day 8 to day of discharge or in-hospital mortality (Model 2) ~~than the AOR of mortality for~~

the no-lipid group. It is possible that tThe small sample size of the ILE-only group relative to the nNo-lipid group was the reason a might lead that a significant difference was not found between those 2 subgroups for in-hospital mortality.

In our study, only 1,614 (7.8%) patients (excluding those who had only propofol prescribed) had ILE prescribed during days 4 through 7 of ICU admission. The limited clinical use of ILE in Japan is likely related to the market conditions in the country. In Japan, 3-in-1 bag formulations, which contain carbohydrates, amino acids, and lipid are rarely available, and so the only available lipid comes in the form of SO ILE. This lipid has a high relative content of n-6 unsaturated fatty acids, which has been reported to increase inflammatory reactions in critically ill patients [1]. Thus, clinicians in Japan may be avoiding the use of SO ILE, especially in patients admitted to the an ICUs. However, use of either SO ILE or Mixed-oil ILE (containing medium-chain triglycerides, olive oil, fish oil, or mixtures of oils) is recommended during the 1st first week of ICU admission for critically ill patients in the nutritional guidelines in critically ill patients of the American Society for Parenteral and Enteral Nutrition [4]. And, our study showed a significant association between SO ILE being prescribed during days 4 through 7 of an ICU admission and a decrease in in-hospital mortality. Thus, even if ILE contains soybean oil, strong consideration should be given by clinicians to using this as part of PN in critically ill patients.

This study has several limitations. First, the patient characteristics used were based on information registered inextracted from a medical claims database, which may have contained entry errors or have had missing data. The primary diseases of patients were coded with ICD-10 retrospectively, which is inferior towhereas the characterization ofing diagnoses prospectively is usually preferred. On the other hand, CCI was also applied retrospectively as a measure of comorbidities, and which has beenit has been validated approach in Japan as and is considered an accurate and reliable and accurate methodapproach to characterize comorbidities [1822]. Second, we were unable to include characteristics pertaining to acute physiology, chronic health conditions, and disease severity, such as the acute physiology and chronic health evaluation II score [1923] or the sequential organ failure assessment score [240], because laboratory data were not included in the database. To work around this, we extracted information about in-hospital prescriptions, treatments, and surgery, and we included the CCI, BI, and JCS for most patients. Then, to help determine whether disease severity impacted our study endpoints, we adjusted our regression analyses using all of these characteristics. However, unknown or residual confounding factors may still have existed. In addition, the nutrition doses might be overestimated because the remained and discarded amount after administration to patients was not considered. Finally, our results may not be possible to generalize to patients in other countries or those receiving more robust parenteral nutritional management. There are several reasons are as followsfor this. Because the only lipid that is clinically available in Japan is soybean-oil based, and propofol contains soybean oil alone or in combination with medium-chain fatty acids, our study did not include any other lipids, such as olive or fish oil, which are available in other countries. In addition, the prescribed doses of energy, amino acids, and lipid doses in our study were relatively low, particularly relative compared withto the doses recommended recommendations in guidelines. Also, all of our patients were fasting for longer than 7 days and a large proportion of our patients were elderly (over 30% ≥ were 80 years old or older) or had a low BMI (over 20% with BMI ≤ of 18.5 or less). These areThese types of baseline characteristics related to disease and nutritional conditions which may be more common and/or worse in patients in Japanese ICUs and worse than in critically ill patients involved in European and American studies.

5. Conclusions

The addition of ILE for days 4 to 7 prescribed for critically ill patients who were in ~~the~~ an ICU~~s~~ receiving mechanical ventilation and fasting for more than 7 days was associated with a significant reduction of in-hospital mortality. No significant differences were observed for hospital readmission or hospital LOS.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, **Table S1:** Classification of primary diagnoses; **Table S2:** Classification of surgical procedures.

Author Contributions: Conceptualization, H.Y., Y.H., S.K., and A.K.; methodology, H.Y., Y.H., S.K., A.K., and T.M.; investigation, H.Y., Y.H., S.K., and A.K.; data curation, H.Y., Y.H., S.K., and A.K.; writing—original draft preparation, H.Y., Y.H., S.K., A.K., and T.M.; writing—review and editing, H.Y., S.K., A.K., and T.M.; project administration, SK. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was ~~conducted after receiving a~~ reviewed ~~by and obtaining the approval~~and approved by ~~of~~ the Institutional Review Board for clinical studies at Saitama Medical Center of Jichi Medical University (Approval Number Rin S20-117). Also, thi~~s~~e study ~~was conducted after being~~ has been registered in the clinical study registration system in the University Hospital Medical Information Network (UMIN) clinical trial registry (Japan) (UMIN000042607). This manuscript complies with the applicable guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology statement [10].

Informed Consent Statement: Informed consent for thi~~s~~e study ~~could not be~~was not obtained because the database used ~~for the study~~ was anonymized.

Data Availability Statement: The data supporting the findings of this study are available from Otsuka Pharmaceutical Factory, Inc. Some restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. ~~However, data~~Data are available from the authors upon reasonable request and with the permission of Otsuka Pharmaceutical Factory, Inc.

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Conflicts of Interest: H. Yasuda received lecture fees from Otsuka Pharmaceutical Factory, Inc. Y. Horikoshi, S. Kamoshita, and A. Kuroda report personal fees received from Otsuka Pharmaceutical Factory, Inc. which were unrelated to the submitted work. T. Moriya declare no competing interests.

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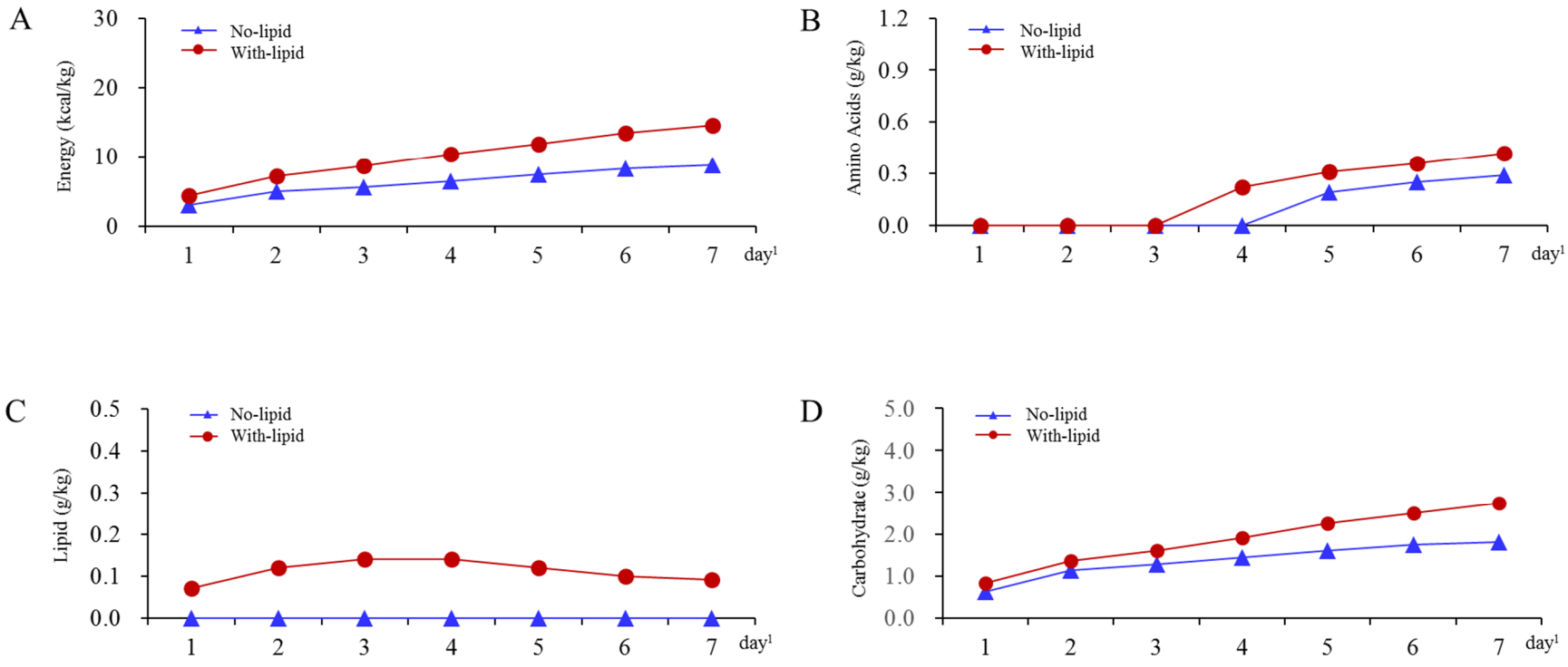
A
Energy (kcal/kg)
30
20
10
0
No-lipid
With-lipid
1
2
3
4
5
6
7
day1
B
Amino Acids (g/kg)
1.2
0.9
0.6
0.3
0.0
No-lipid
With-lipid
1
2
3
4
5
6
7
day1
C
Lipid (g/kg)
0.5
0.4
0.3
0.2
0.1
0.0
No-lipid
With-lipid
1
2
3
4
5
6
7
day1
D
Carbohydrate (g/kg)
5.0
4.0
3.0
2.0
1.0
0.0
No-lipid
With-lipid
1
2
3
4
5
6
7
day1

Supplementary Table 1 Classification of primary diagnoses

Diagnosis	International Classification of Diseases, 10th revision (ICD-10) Codes
Sepsis	A02.1, A20.7, A22.7, A26.7, A32.7, A40-A41, A42.7, B37.7
Neoplasms	C00-D48, excluding D10-D36
Diseases of the nervous system	G00-G99
Ischemic heart disease	I20-I25
Heart failure	I50
Cerebrovascular diseases	I60-I69
Other circulatory system diseases	I00-I49, I51-I52, I70-I99
Pneumonia	J10.0、J11.0、J12-J18、J85.1
Interstitial respiratory diseases	J80-J84
Other respiratory diseases	J00-J09、J10.1-J10.8、J11.1-J11.8、J20-J70、J85.0、J85.2-J85.3、J86-J99
Diseases of the digestive system	K00-K93
Kidney diseases	N00-N29
Injury, poisoning and certain other consequences of external causes	S00-S99, T00-T14, T20-T65
Other	Other than above

Supplementary Table 2 Classification of surgical procedures

Category of Surgery	Japan-specific Surgical Codes
Cardiovascular	K538-K6105, K613-K6173, K619-628, Excluding K601 and K602
Gastroenterological	K5201-K5372, K630-K663, K665-K7424
Cerebrovascular	K145-K181
Respiratory	K488-K5181
Orthopedic	K023-K144
Urological/Gynecological	K757-K8903
Multiple surgeries	More than one surgery in categories above
Other	Excluding above categories, K601, and K602
No surgery	Not applicable to any of codes above, or **no** record of surgery under general or lumber spinal anesthesia

Supplementary Table 3 Characteristics of patients by subgroups

Characteristics	Categories	Patient Subgroups		
		ILE-only	ILE+ propofol	Propofol-only
		n = 1073	n = 541	n = 6847
Age, *years*, n (%)	< 60	124 (11.6)	78 (14.4)	1,511 (22.1)
	60–69	176 (16.4)	114 (21.1)	1,473 (21.5)
	70–79	348 (32.4)	184 (34.0)	2,144 (31.3)
	80–89	346 (32.2)	139 (25.7)	1,545 (22.6)
	g 90	79 (7.4)	26 (4.8)	174 (2.5)
Sex, n (%)	Male	702 (65.4)	391 (72.3)	4,585 (67.0)
	Female	371 (34.6)	150 (27.7)	2,262 (33.0)
Body mass index, *kg/m* ², n (%)	< 16	122 (11.4)	40 (7.4)	277 (4.0)
	16–18.5	193 (18.0)	83 (15.3)	751 (11.0)
	18.5–22.5	389 (36.3)	201 (37.2)	2,365 (34.5)
	22.5–25	193 (18.0)	110 (20.3)	1,592 (23.3)
	g 25	176 (16.4)	107 (19.8)	1,862 (27.2)
Beds in admission hospital, n (%)	< 200	37 (3.4)	21 (3.9)	304 (4.4)
	g 200g g 500	677 (63.1)	288 (53.2)	3,776 (55.1)
	g 500	359 (33.5)	232 (42.9)	2,767 (40.4)
Admission year, n (%)	2010–2011	36 (3.4)	19 (3.5)	244 (3.6)
	2012–2013	119 (11.1)	83 (15.3)	648 (9.5)
	2014–2015	214 (19.9)	104 (19.2)	1,452 (21.2)
	2016–2017	277 (25.8)	151 (27.9)	2,057 (30.0)

	2018–2019	363 (33.8)	163 (30.1)	2,116 (30.9)
	2020	64 (6.0)	21 (3.9)	330 (4.8)
Primary diagnosis[1], n (%)	Sepsis	64 (6.0)	34 (6.3)	472 (6.9)
	Neoplasm	167 (15.6)	94 (17.4)	803 (11.7)
	Diseases of the nervous system	33 (3.1)	12 (2.2)	170 (2.5)
	Ischemic heart disease	29 (2.7)	20 (3.7)	644 (9.4)
	Heart failure	44 (4.1)	9 (1.7)	287 (4.2)
	Cerebrovascular disorders	63 (5.9)	32 (5.9)	652 (9.5)
	Other circulatory system diseases	97 (9.0)	78 (14.4)	1,428 (20.9)
	Pneumonia	64 (6.0)	20 (3.7)	173 (2.5)
	Interstitial respiratory diseases	32 (3.0)	31 (5.7)	170 (2.5)
	Other respiratory diseases	99 (9.2)	20 (3.7)	264 (3.9)
	Diseases of the digestive system	249 (23.2)	115 (21.3)	960 (14.0)
	Kidney diseases	20 (1.9)	5 (0.9)	84 (1.2)
	Injury, poisoning, other consequences external causes	36 (3.4)	18 (3.3)	341 (5.0)
	Other	76 (7.1)	53 (9.8)	399 (5.8)
Charlson Comorbidity Index, n (%)	0	511 (47.6)	266 (49.2)	3,521 (51.4)
	1-2	397 (37.0)	190 (35.1)	2,375 (34.7)
	≥ 3	165 (15.4)	85 (15.7)	951 (13.9)
Barthel Index, n (%)	100	247 (23.0)	151 (27.9)	1,733 (25.3)
	65–95	40 (3.7)	35 (6.5)	237 (3.5)

	45–60	45 (4.2)	15 (2.8)	208 (3.0)
	25–40	15 (1.4)	14 (2.6)	120 (1.8)
	5–20	65 (6.1)	36 (6.7)	241 (3.5)
	0	512 (47.7)	195 (36.0)	3,335 (48.7)
	NA	149 (13.9)	95 (17.6)	973 (14.2)
Japan Coma Scale, n (%)	0	589 (54.9)	325 (60.1)	3,766 (55.0)
	1–3	206 (19.2)	116 (21.4)	1,096 (16.0)
	10–30	99 (9.2)	37 (6.8)	574 (8.4)
	100–300	179 (16.7)	63 (11.6)	1,411 (20.6)
	NA	0 (0.0)	0 (0.0)	0 (0.0)
Surgery[2], n (%)	Cardiovascular	62 (5.8)	59 (10.9)	1,092 (15.9)
	Gastroenterological	366 (34.1)	199 (36.8)	1,544 (22.6)
	Cerebrovascular	40 (3.7)	21 (3.9)	376 (5.5)
	Respiratory	6 (0.6)	3 (0.6)	32 (0.5)
	Orthopedic	4 (0.4)	3 (0.6)	33 (0.5)
	Urological/Gynecological	7 (0.7)	3 (0.6)	31 (0.5)
	Multiple surgeries	6 (0.6)	5 (0.9)	51 (0.7)
	Other	28 (2.6)	19 (3.5)	147 (2.1)
	No surgery	554 (51.6)	229 (42.3)	3,541 (51.7)
Prescription/treatment[3], n (%)	Catecholamines	744 (69.3)	430 (79.5)	5,345 (78.1)
	Transfusion	562 (52.4)	331 (61.2)	4,236 (61.9)
	Albumin	596 (55.5)	361 (66.7)	4,075 (59.5)
	Renal replacement therapy	210 (19.6)	136 (25.1)	1,879 (27.4)

	Intra-aortic balloon pump	35 (3.3)	26 (4.8)	859 (12.5)
	Plasmapheresis	1 (0.1)	4 (0.7)	39 (0.6)
	ECMO	12 (1.1)	19 (3.5)	500 (7.3)
	Nutritional support team	56 (5.2)	32 (5.9)	85 (1.2)
	Rehabilitation[4]	620 (57.8)	278 (51.4)	2,940 (42.9)
Parenteral nutrition[5], median (Q1, Q3)	Energy, *kcal/kg*	14.1 (10.3, 19.1)	15.8 (11.7, 20.4)	9.8 (6.2, 14.5)
	Amino Acid, *g/kg*	0.41 (0.23, 0.59)	0.42 (0.25, 0.61)	0.19 (0.00, 0.38)
	Lipid, *g/kg*	0.19 (0.11, 0.29)	0.28 (0.19, 0.41)	0.12 (0.06, 0.20)
	Carbohydrate, *g/kg*	2.7 (1.8, 3.7)	2.9 (2.0, 3.7)	1.9 (1.1, 2.9)
Days without nutrition from day 8[6]**,** median (Q1, Q3)		0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)

Abbreviations: ECMO, extracorporeal membrane oxygenation; Q1, first quartile; Q3, third quartile.

[1] Diagnoses identified using International Statistical Classification of Diseases and Related Health Problems, 10th revision.

[2] Between day of hospital admission and day of intensive care unit admission, based on Japan-specific codes.

[3] During days 1 to 7 of intensive care unit admission. Day 1 regarded as day of intensive care unit admission.

[4] Feeding therapy and/or rehabilitation for cardiac microvascular, cerebrovascular, disuse syndrome, locomotor, and/or respiratory diseases.

[5] Medians of mean prescribed daily doses during days 1 to 7 of intensive care unit admission.

[6] Days without nutrition (oral intake, enteral nutrition, or parenteral amino acids/lipid) from day 8 to day of discharge or in-hospital death.