JOURNAL CLUB 評讀文獻

- **Early versus Late Parenteral Nutrition in Critically Ill Children**
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背景

- Critically ill children cannot normally be fed by mouth, and as a result a pronounced macronutrient deficit often develops after a few days.
  - This macronutrient deficit has been associated with infections, weakness, prolonged mechanical ventilation, and delayed recovery.
- The preferred route for the administration of nutritional support in the pediatric ICU is the nasogastric tube, but enteral nutrition is often delayed or interrupted.
  - When enteral nutrition fails, parenteral nutrition is advised.
  - With respect to critically ill adults, recent large, randomized, controlled trials have questioned the benefit of early parenteral nutrition. (Casaer et al., 2011)
- Therefore, in this studt, we investigated whether a strategy of withholding parenteral nutrition up to day 8 (late parenteral nutrition) in the pediatric ICU is clinically superior to the current practice of early parenteral nutrition.

Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011; 365: 506-17.

步驟 1：研究探討的問題為何？

- **研究族群 / 問題 (Population/ Problem)**
  - children (from term newborns to children 17 years of age) who were admitted to one of the participating pediatric ICUs
- **介入措施 (Intervention)**
  - late-parenteral-nutrition group, parenteral nutrition was withheld up to the morning of day 8 in the pediatric ICU.
- **比較 (Comparison)**
  - early parenteral nutrition, parenteral nutrition was initiated within 24 hours after admission to the pediatric ICU.
- **結果 (Outcomes)**
  - (next page)

步驟 1：研究探討的問題為何？

- 結果 (Outcomes)
  - **Primary outcome**
    - ✓ new infection acquired during the ICU stay
    - ✓ the duration of ICU dependency.
  - **Secondary outcomes**
    - ✓ Odds for death
    - ✓ the number of patients with hypoglycemia
    - ✓ the number of readmissions to the pediatric ICU within 48 hours after discharge
    - ✓ the time to final (live) weaning from mechanical ventilatory support
    - ✓ the duration of pharmacologic or mechanical hemodynamic support
    - ✓ the proportion of patients receiving renal-replacement therapy
    - ✓ markers of liver dysfunction and inflammation
    - ✓ the time to (live) discharge from the hospital

步驟 2：研究的品質有多好(內在效度)？

招募(Recruitment) - 受試者是否具有代表性？	
最好的狀況是？	我可以在哪裡找到這些資訊？
我們是否知道病人族群為何(收案場所、納入 / 排除條件)？在理想情況下，納入本研究之受試者應具有連續性(有時為隨機取樣)，了解符合收案條件的對象且簽署同意書。	在文章的**方法(Methods)**章節的開頭，可以找到本研究篩選病人的方式。
評讀結果 ☑是 ☐否 ☐不清楚 說明：	

- From June 18, 2012, through July 27, 2015,
- all children (from term newborns to children 17 years of age)
- who were admitted to one of the participating pediatric ICUs were eligible for inclusion
- if a stay of 24 hours or more in the ICU was expected
- if they had a score on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) of 2 or more
  - (with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk)
- and if none of the criteria for exclusion were met

Supplementary Table 1. *Exclusion criteria for study participation*

Not critically ill enough to necessitate nutritional support
STRONGkids score lower than 2 on PICU admission[1]
Non-pediatric patients (aged 17 or older)
Premature newborns (<37 weeks gestational age upon admission in the PICU)
'Do not resuscitate' code at the time of PICU admission
Expected death within 12 hours
Readmission to PICU after already having been randomized
Enrollment in another intervention trial
Transfer from another PICU or neonatal ICU after a stay of more than 7 days
Ketoacidotic or hyperosmolar coma
Inborn metabolic diseases requiring specific diet
Short bowel syndrome or other conditions requiring PN for more than 7 days prior to PICU admission

PICU=Pediatric Intensive Care Unit, PN=Parenteral Nutrition

TABLE 1

FROM:
Nutritional screening and guidelines for managing the child with faltering growth
K Joosten and R Meyer

BACK TO ARTICLE

Table 1. STRONGkids (screening tool for risk of nutritional status and growth)

▲ Figure and tables index | Next table ▸

(1) Subjective clinical assessment (1 point)
Is the patient in a poor nutritional status judged by subjective clinical assessment (diminished subcutaneous fat and/or muscle mass and/or hollow face)?
(2) High-risk disease (2 points)
Is there an underlying illness with a risk of malnutrition or expected major surgery?
(3) Nutritional intake and losses (1 point)
Are there any of the following items present?
Excessive diarrhoea (⩾5 per day) and/or vomiting (>3 times/day) the last few days?
Reduced food intake during the last few days before admission (not including fasting for an elective procedure or surgery)?
Pre-existing dietetically advised nutritional intervention?
Inability to consume adequate intake because of pain?
(4) Weight loss or poor weight gain? (1 point)
Is there weight loss or no weight gain (infants <1 year) during the last few weeks/months?

▲ Figure and tables index | Next table ▸

BACK TO ARTICLE

步驟 2：研究的品質有多好(內在效度)？

招募(Recruitment) - 受試者是否具有代表性？	
最好的狀況是？	我可以在哪裡找到這些資訊？
我們是否知道病人族群為何(收案場所、納入 / 排除條件)？在理想情況下，納入本研究之受試者應具有連續性(有時為隨機取樣)，了解符合收案條件的對象且簽署同意書。	在文章的**方法(Methods)**章節的開頭，可以找到本研究篩選病人的方式。
評讀結果：☑是　☐否　☐不清楚　說明：	

- Written informed consent was requested from parents or legal guardians before elective admission to the pediatric ICU.
- For emergency admissions, consent was requested within 24 hours after the child's admission to the pediatric ICU.
- The institutional review board at each participating site approved the protocol.

分派(Allocation) - 分派方式是否隨機且具隱匿性... ？	
最好的狀況是？	我可以在哪裡找到這些資訊？
最理想的方式是以中央電腦進行隨機分配，此方式常用於多中心試驗，而較小型的試驗可由獨立人員(如醫院藥師)「監督」隨機分配的過程。	在文章的**方法(Methods)**段落中，可以找到病人分配到不同組的方式，以及隨機分配是否具隱匿性；作者應說明隨機分派方式「監督」或屏蔽(masking)的方式(如使用外觀相同的安慰劑、或給予一個「假的」治療 sham therapy）。
評讀結果 ☑是 ☐否 ☐不清楚 說明：	

- At each center, consecutive, eligible patients were randomly assigned to one of the two treatment groups in a 1:1 ratio.
- Concealment of group assignment was ensured by the use of a central computerized randomization system.

...每個組別，在研究開始時的情況是否相同？	
最好的狀況是？	我可以在哪裡找到這些資訊？
若隨機分配順利，各組研究對象的條件應是相近、可互相比較的。每組研究對象的基本條件越相近越好。應有指標可確認各組研究對象之間的差異是否達到統計上顯著的差異(如 p 值)。	在文章的**結果(Results)** 段落中，可以找到「研究對象基本資料」的表格，裡面包括幾個可能影響隨機分配的各組研究結果之重要變項(如年齡、風險因子等)。如果作者沒有用表格呈現，在**結果**章節的第一段中，可能可以找到各組研究對象特性的說明。
評讀結果：☑是　☐否　☐不清楚　說明：	

- At baseline, the characteristics of the patients were similar in the two groups (Table 1).

Table 1. Baseline Characteristics.*

Characteristic	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)
Median age (IQR) — yr	1.4 (0.3 to 6.1)	1.5 (0.2 to 7.2)
Age <1 yr — no. (%)	328 (45.4)	325 (45.3)
Male sex — no. (%)	415 (57.4)	415 (57.9)
Median weight (IQR) — kg	10.0 (4.8 to 20.0)	10.3 (4.5 to 21.5)
Median standard deviation score (IQR)†	−0.5 (−1.4 to 0.5)	−0.4 (−1.4 to 0.5)
Median height (IQR) — cm	80 (58 to 113)	80 (56 to 120)
Median standard deviation score (IQR)†	−0.3 (−1.5 to 0.8)	−0.3 (−1.4 to 0.8)
Median BMI (IQR)	15 (14–17)	15 (14–17)
Median standard deviation score (IQR)†	−0.5 (−1.5 to 0.5)	−0.5 (−1.6 to 0.6)
STRONGkids risk level — no. (%)‡		
Medium	644 (89.1)	644 (89.8)
High	79 (10.9)	73 (10.2)
Median PELOD score, first 24 hr in pediatric ICU (IQR)§	21 (11 to 31)	21 (11 to 31)
Emergency admission — no. (%)	383 (53.0)	400 (55.8)
Diagnostic group — no. (%)		
Surgical		
Abdominal	53 (7.3)	60 (8.4)
Burns	5 (0.7)	5 (0.7)
Cardiac	279 (38.6)	268 (37.3)
Neurosurgery–traumatic brain injury	63 (8.7)	53 (7.3)
Thoracic	34 (4.7)	27 (3.8)
Transplantation	7 (1.0)	17 (2.4)
Orthopedic surgery–trauma	28 (3.9)	26 (3.6)
Other	21 (2.9)	27 (3.8)
Medical		
Cardiac	30 (4.1)	31 (4.3)
Gastrointestinal–hepatic	2 (0.3)	4 (0.6)
Oncologic–hematologic	8 (1.1)	7 (1.0)
Neurologic	51 (7.1)	52 (7.3)
Renal	1 (0.1)	1 (0.1)
Respiratory	99 (13.7)	96 (13.4)
Other	42 (5.8)	43 (6.0)
Condition on admission — no. (%)		
Mechanical ventilation required	639 (88.4)	622 (86.8)
ECMO or other assist device required	19 (2.6)	25 (3.5)
Infection	287 (39.7)	271 (37.8)

* There were no significant differences in characteristics between treatment groups at baseline. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), ECMO extracorporeal membrane oxygenation, and ICU intensive care unit.

Organization.[18]

‡ Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

§ Pediatric Logistic Organ Dysfunction (PELOD) scores range from 0 to 71, with higher scores indicating more severe illness.

維持(Maintenance) - 各組是否給予相同的治療？	
最好的狀況是？	我可以在哪裡找到這些資訊？
各研究組別之間，除了對病人的介入之外，其餘的治療應完全相同(即為了執行本研究所增加的治療、檢驗或評估應相同)。	在文章的**方法**段落中，可以找到各組詳細的治療方式(如追蹤時間表、研究中可以使用的額外治療），在**結果**段落中，應該也可以找到更進一步的資訊。
評讀結果：☑是 ☐否 ☐不清楚 說明：	

- In both study groups, enteral nutrition was initiated early and was increased in accordance with local guidelines.
- Both study groups also received intravenous micronutrients (trace elements, minerals, and vitamins) starting from day 2 and continuing until the enteral nutrition provided reached 80% of the caloric targets.
- Starting from the morning of day 8 in the pediatric ICU, supplementary parenteral nutrition was provided for patients in both groups who were not yet receiving 80% of the caloric target enterally.

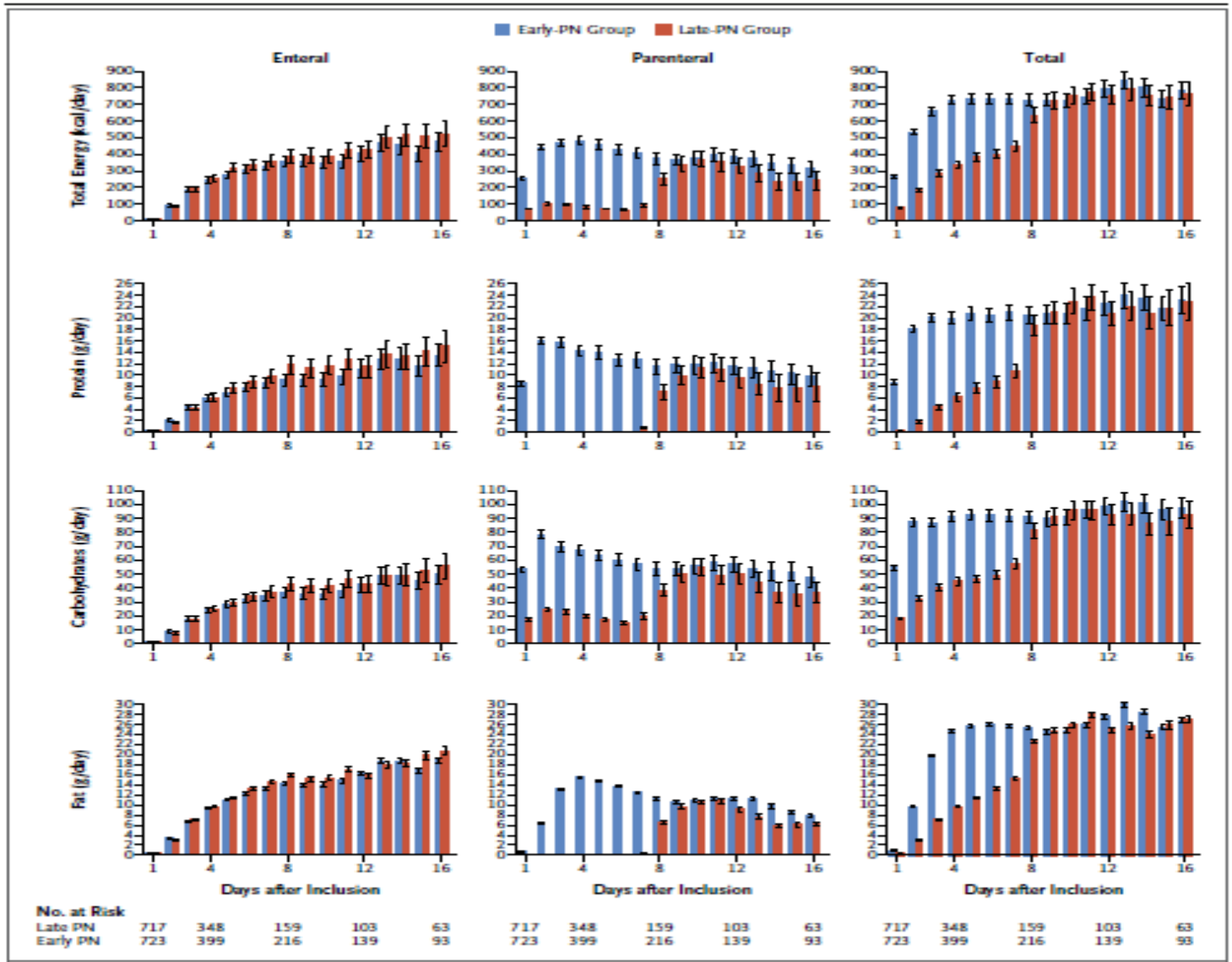

Figure 2. Daily Caloric and Macronutrient Intake.

The daily amount of energy (kilocalories per day) and substrate (grams per day) provided by the enteral route, the parenteral route, or both (total) are shown for participants' first 16 days in the pediatric intensive care unit (ICU). I bars indicate the standard error. PN denotes parenteral nutrition.

…是否有足夠的追蹤(Follow up)？	
最好的狀況是？	我可以在哪裡找到這些資訊？
研究中流失(無法繼續追蹤)的病人，最好少於 20%。病人應依照隨機分配的組別進行統計分析(即「治療意向分析法」Intention – to-treat , ITT analysis)。	在文章的**結果**段落中，應可以找到接受隨機分配的病人人數，以及實際進行分析的人數。有時會有流程圖(如果沒有，可自行繪製)。
評讀結果：☑是 ☐否 ☐不清楚 說明：	

- A total of 1440 patients underwent randomization and were included in the analysis.
- All analyses were conducted on an intention-to-treat basis.

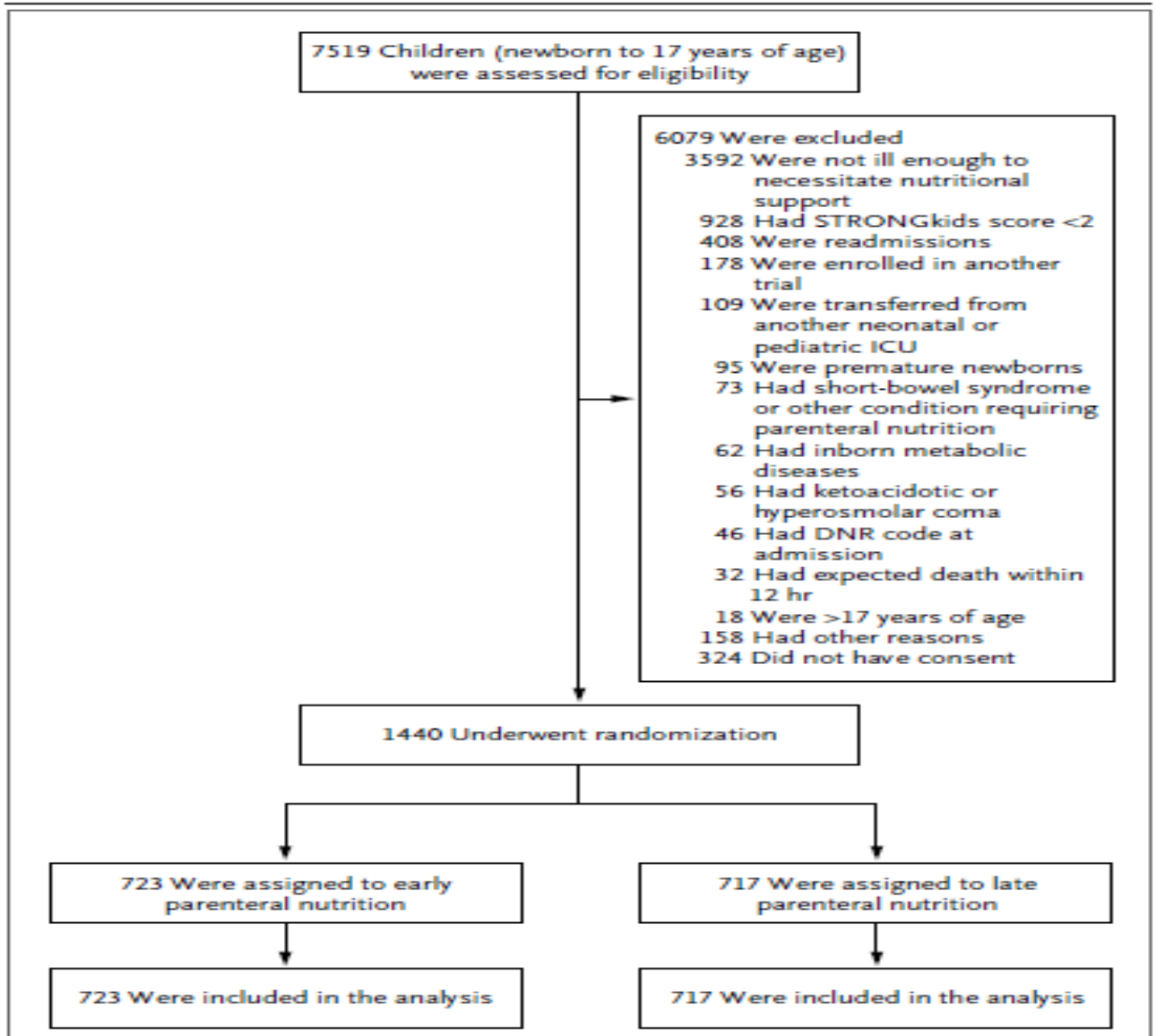

Figure 1. Screening and Randomization.

The scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.[17] DNR denotes do not resuscitate, and ICU intensive care unit.

評估(Measurement) - 受試者與評估者是否對治療方式及(或)評估目的維持盲法(blind)？	
最好的狀況是？	我可以在哪裡找到這些資訊？
在客觀結果(如：死亡)方面，盲法的重要性較低，但在主觀結果(如：症狀或功能)方面，評估者維持盲法非常重要。	在文章的**方法**段落中，可以找到研究結果的評估方式，以及評估者是否知道病人接受何種治療。
評讀結果：☐是 ☑否 ☐不清楚 說明：	

- The patients, their parents, and the staff providing intensive care were aware of the treatment assignments.
- Outcome assessors and investigators who were not directly involved in ICU patient care were unaware of the treatment assignments.

步驟 3：研究結果及討論

研究結果[1]

Outcome	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)	P Value	Adjusted Odds Ratio or Hazard Ratio (95% CI)†	P Value
Primary					
New infections — no. (%)	134 (18.5)	77 (10.7)	<0.001	0.48 (0.35–0.66)‡	<0.001
Airway	59 (8.2)	30 (4.2)	0.002		
Bloodstream	23 (3.2)	10 (1.4)	0.03		
Urinary tract	7 (1.0)	2 (0.3)	0.17		
Central nervous system	3 (0.4)	2 (0.3)	1.00		
Soft tissue	7 (1.0)	4 (0.6)	0.54		
Other focus	5 (0.7)	8 (1.1)	0.42		
No focus identified	30 (4.1)	21 (2.9)	0.25		
Total duration of antibiotic treatment for patients with new infection — days	21.3±3.1	17.4±1.9	0.77		
Total duration of stay in pediatric ICU — days§	9.2±0.8	6.5±0.4	0.002	1.23 (1.11–1.37)	<0.001
Patients requiring ≥8 days in pediatric ICU — no. (%)	216 (29.9)	159 (22.2)	<0.001		

步驟 3：研究結果及討論

研究結果[2]

Outcome	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)	P Value	Adjusted Odds Ratio or Hazard Ratio (95% CI)†	P Value
Secondary					
Safety					
Death — no. (%)					
Within 8 days of admission to pediatric ICU	21 (2.9)	19 (2.6)	0.87	0.73 (0.34–1.51)‡	0.39
During stay in pediatric ICU	36 (5.0)	32 (4.5)	0.70	0.73 (0.42–1.28)‡	0.27
During hospital stay	44 (6.1)	37 (5.2)	0.49	0.72 (0.43–1.19)‡	0.20
Within 90 days after enrollment	49 (6.8)	38 (5.3)	0.26	0.64 (0.39–1.05)‡	0.08
Hypoglycemia: glucose <40 mg/dl during first 7 days in pediatric ICU — no. (%)	35 (4.8)	65 (9.1)	0.001		
Hypoglycemia refractory to treatment for ≥2 hr — no. (%)	0	1 (0.1)	1.00		
Readmission to pediatric ICU within 48 hr after discharge — no. (%)	9 (1.2)	13 (1.8)	0.39		

步驟 3：研究結果及討論

研究結果[3]

Outcome	Early Parenteral Nutrition (N=723)	Late Parenteral Nutrition (N=717)	P Value	Adjusted Odds Ratio or Hazard Ratio (95% CI)†	P Value
Efficacy					
Duration of mechanical ventilatory support — days	6.4±0.7	4.4±0.3	0.01	1.19 (1.07–1.32)	0.001
Duration of hemodynamic support — days	3.0±0.3	2.4±0.2	0.35		
Kidney failure with renal-replacement therapy — no. (%)	26 (3.6)	18 (2.5)	0.28	0.49 (0.24–0.96)‡	0.04
Liver dysfunction during first 7 days in pediatric ICU¶					
Highest plasma level of total bilirubin — mg/dl	1.5±0.1	1.7±0.1	0.003		
Highest plasma level of alkaline phosphatase — IU/liter	171±3	171±5	0.04		
Highest plasma level of γ-glutamyltransferase — IU/liter	58±6	45±3	0.001		
Highest plasma level of alanine aminotransferase — IU/liter	72±8	113±20	0.64		
Highest plasma level of aspartate aminotransferase — IU/liter	179±26	262±48	0.76		
Highest plasma level of C-reactive protein during first 7 days in pediatric ICU, as measure of inflammation — mg/liter	79±4	90±4	0.007		
Duration of hospital stay — days					
Index hospital	21.3±1.3	17.2±1.0	0.005	1.19 (1.07–1.33)	0.001
Index and transfer hospital	22.6±1.3	18.6±1.0	0.01	1.21 (1.08–1.34)	<0.001

MAIN RESULTS

- The results of our trial showed that withholding parenteral nutrition for 1 week in the pediatric ICU was clinically superior to providing early parenteral nutrition; late parenteral nutrition resulted in fewer new infections, a shorter duration of dependency on intensive care, and a shorter hospital stay.
- The clinical superiority of late parenteral nutrition was shown irrespective of diagnosis, severity of illness, risk of malnutrition, or age of the child.

★討論 (本研究是否可用於臨床?)

- 目前國內相關研究不多，兩篇2014年針對成人的研究，不建議早期給予靜脈營養
- 依院內目前規範，若預期5~7天無法提供腸道營養，就會給予腸外營養
- 但大手術後或病人生命徵象不穩定，給予腸外營養，會有感染等的風險
- 在台灣，延遲到第8天才開始給予腸外營養，家屬恐無法接受，而可能產生糾紛

★討論 (本研究是否可用於臨床?)

- 在能提供腸道營養的前提下，若熱量仍不足夠，是否支持延遲至第8天才給予腸外營養？

仍有爭議：

36票

THANK YOU!