Identification of risk factors for enteral feeding intolerance screening in critically ill patients

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ABSTRACT

الأهداف: لتحديد عوامل الخطر لفحص عدم تحمل التغذية المعوية في المرضى ذوي الحالات الحرجة، وبالتالي، توفير بعض المراجع لموظفي الرعاية الصحية لتقييم مخاطر عدم تحمل التغذية، ووضع الأساس لمستوى التنمية في المستقبل.

الطريقة: أجريت دراسة منهجية مختلطة، بما في ذلك استعراض الأدب ومقابلات شبه منظمة، وتقنية دلفي، وعملية التحليل الهرمي. استخدمنا مراجعة الأدبيات ومقابلات شبه منظمة (n=22) لتجميع صياغة البنود المبدئية لعدم تحمل التغذية وتقنية دلفي (n=30) للكشف وتحديد البنود، وعملية التحليل الهرمي لحساب وزن كل عنصر. أجريت الدراسة خلال الفترة من يونيو 2014م حتى سبتمبر 2015م في مستشفى دابينغ، جامعة وتشونغتشينغ الثالثة الطبية العسكرية، الصين.

النتائج: وقد تم اختيار٢٣ عوامل الخطر على نطاق واسع، بما في ذلك 5 أبعاد. قمنا بتعيين الوزن إلى كل بند وتأثيرها على عدم تحمل التغذية، مع زيادة درجة مبينا تأثير أكبر. وزن كل البعد الذي يقل على النحو التالي: حالة المريض، نتيجة الوزن تساوي 42؛ والشروط العامة نتيجة الوزن تساوي 23؛ وظائف الجهاز الهضمي، نتيجة الوزن تساوي 15؛ والمؤشرات الكيميائية الحيوية، نتيجة الوزن تساوي 14؛ والتدابير العلاجية، نتيجة الوزن تساوي ٦.

الخاتمة: تطوير عوامل الخطر القائمة استناداً إلى المراجعات الأدبية، المسح للمختصين في الرعاية الصحية، واستطلاع الخبراء يجب أن يوفر أساس للدراسات المستقبلية لتقييم خطر عدم تحمل التغذية المعوية في المرضى ذوي الحالات الحرجة.

Objectives: To identify risk factors for enteral feeding intolerance screening in critically ill patients, thereby, provide some reference for healthcare staff to assess the risk of feeding intolerance, and lay the foundation for future scale development.

Methods: This study used a mixed methodology, including a literature review, semi-structured interviews, the Delphi technique, and the analytic hierarchy process. We used the literature review and semi-structured interviews (n=22) to draft a preliminarily item pool for feeding intolerance, Delphi technique (n=30) to screen and determine the items, and the analytic hierarchy process to calculate the weight of each item. The study was conducted between June 2014 and September 2015 in Daping Hospital, Third Military Medical University, Chongqing, China.

Results. Twenty-three risk factors were selected for the scale, including 5 dimensions. We assigned a weight to each item according to their impact on the feeding intolerance, with a higher score indicating a greater impact. The weight of each dimension was decreasing as follows: patient conditions, weight score equals 42; general conditions, weight score equals 23; gastrointestinal functions, weight score equals 15; biochemical indexes, weight score equals 14; and treatment measures, weight score equals 6.

Conclusion. Developed list of risk factors based on literature review, survey among health care professionals and expert consensus should provide a basis for future studies assessing the risk of feeding intolerance in critically ill patients.

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Feeding intolerance (FI) is a general term that indicates an intolerance of enteral nutrition (EN) feeding for any clinical reason, including vomiting, high gastric residual, diarrhea, gastrointestinal bleeding, and the presence of entero-cutaneous fistulas.[1] Feeding intolerance occurs a median 3 days after EN initiation with an incidence of 30.5%, resulting in poor outcomes and nutrition.[2] Recently, factors influencing FI have been studied in detail. For instance, edema of the gastrointestinal mucosa may occur in conjunction with low serum albumin levels, which can compromise gastrointestinal digestion and the absorption barrier.[3] Nguyen et al[4] found that patients with blood glucose levels greater than 10.0mmol/L were more susceptible to FI, and Camilleri et al[5] noted that blood glucose levels greater than 11.1 mmol/L could aggravate gastroparesis symptoms and delay gastric emptying. Additionally, mechanical ventilation, especially in patients with positive end-expiratory pressure, can cause gastrointestinal tract ischemia and induce FI.[6,7] The aforementioned studies suggested that the occurrence of FI was affected by many risk factors. Therefore, healthcare staff need to be able to assess the risk of FI occurrence by comprehensively analyzing various indicators, including the patient's disease and physiology. However, because no measurement tool enabling the early detection of FI risk currently exists, different healthcare staff subjectively judge these risks based on their professional knowledge and clinical experience; thus, differences in specializations of knowledge and practical experiences directly affect the accuracy and consistency of the assessments. Therefore, we aimed to identify and determine the weights of items for inclusion in a FI risk assessment scale, decrease the influence of differences in professional knowledge and clinical experience and provide a foundation for further scale development.

Methods. In this study, we adopted 3 methods (a literature review, semi-structured interviews, and the Delphi technique) to identify and select scale items and used the analytic hierarchy process (AHP) to establish the item weights. The 4 methods were performed in 3 phases. In phase 1, a literature review and semi-structured interviews were used to extract risk factor data from existing studies and to identify risk factors known to the intensive care unit (ICU) healthcare staff for the construction a pool of potential risk factor items. In phase 2, 2 rounds of the Delphi technique were applied to screen and identify items for inclusion. In phase 3, the AHP was used to establish the weight of each included item based on expert consensus.

Data collection. In phase 1, we searched the relevant literature to identify risk factors using the following search terms: "enteral nutrition" and "feeding intolerance", "feeding intolerance", "enteral nutrition" and "gastrointestinal dysfunction", "gastrointestinal dysfunction", and "intestinal dysfunction". Articles were identified from 2 sources: 1) a search on PubMed, Web of science, Medline, CNKI (China National Knowledge Infrastructure) VIP (VIP Database for Chinese Technical Periodicals) databases and 2) the screening of references from the identified articles.

The inclusion criteria for the articles were articles involving FI or gastrointestinal dysfunction or disorder-related EN. The exclusion criteria for the articles were articles on infant feeding intolerance, or articles on the effect of EN in patients with gastrointestinal or barrier function disorders diseases without covering anything about FI in content.

Data were collected between June 2014 and October 2014. Simultaneously, a purposive sampling method was used according to the preliminary interview protocol to recruit healthcare staff employed in the ICU of a tertiary hospital in Chongqing City to participate in semi-structured interviews regarding factors that may increase the patient risk of FI. The interview protocol addressed the following factors: 1) work experience (years) of the participants; 2) perceived factors that may lead FI; and 3) measures the participants have taken to prevent FI. Data were collected between November 2014 and January 2015. Following recruitment, 22 participants were enrolled, including 4 doctors and 18 nurses; the sample size was determined according to the principle of Information Saturation.[8,9] The participants were required to have experience administering enteral nutrition in the ICU. The average duration of working experience among these participants was 8.36 (SD 4.45) years. Interview data were recorded using audio recording or note taking, and the audio recordings were transcribed into text following the interview.

In phase 2, we obtained expert consultations (questionnaire by e-mail) regarding the correlations between the items and the FI occurrence to ensure the representativeness of the scale items. The items were classified according to the World Health Organization (WHO) Life Quality Scale (Chinese Version) into the following categories: not related (1 point), slightly related (2 points), relevant (3 points), more relevant (4 points), and extremely relevant (5 points). In total, 33 experts were preliminarily recruited from 16 tertiary hospitals in Beijing, Shanghai, 6 other provinces and 3 municipalities in China. The inclusion criteria for the experts were as follows: intermediate and above

professional title, at last 8 years practicing EN-related clinical care in the ICU of a tertiary hospital, and willingness to participate in this study. The exclusion criteria for the experts was the inability to guarantee completion of the entire consultation process. The included experts did not discuss or exchange views with one another. Additionally, the questionnaire included columns titled "suggestions for revision" and "additional data are needed" to fully collect expert opinions on alternative projects. The data were collected from January 2015 to September 2015.

In phase 3, the item weights were determined using the AHP based on the identified FI risk factors and the expert scoring results. Specifically, pairwise comparisons of the experts' scoring of each item were performed to determine the relative importance score value of each item and construct a judgment matrix. Finally, the consistency in the expert consultation questionnaire responses was checked, and the weights of the items were determined (**Table 1**).

Data analysis. Due to the small sample size and interviewee number, the semi-structured interview results were analyzed using artificial coding. Risk factors that were directly mentioned or implied by the healthcare staff were counted, and the frequency of each item was calculated relative to the total results. Microsoft Office Excel 2007 was used for data management and IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp.) was used for the statistical analysis. The mean item score and the coefficient of variation were calculated for descriptive statistics. Items were considered for removal if their mean score was ≤3 and their coefficient of variation was ≥0.3.[10,11] Then, these items were selected based on the group discussion results. The group consisted of 3 EN experts employed in the ICU with senior or above professional titles (2 doctors and 1 nurse) and all members of the research group (1 professor, 3 master's degree candidates, and 7 doctoral candidates). The recovery rates of the questionnaire, the expert authority coefficient, and Kendall's coefficient of concordance were calculated to analyze the reliability of the expert consultation results; a p value less than 0.05 was considered significant. The consistency of each questionnaire tested in the AHP and a random consistency ratio (CR) less than or equal to 0.1 were considered a passing score for the consistency test.[12] All questionnaires that passed the test were used to independently calculate the weight coefficients of each item. The mean weight coefficient of the same item represents the weight of this item.

Ethical considerations. This study was approved by the Ethics Committee of the Third Affiliated Hospital (Daping Hospital), Third Military Medical University, Chongqing, China. All participants signed informed consent before the beginning of the semi-structured interviews, and all materials were kept confidential, including the audio recordings, the interview conversation content, and the personal information of the interviewees. Participation was voluntary, and the participants had the right to reject or discontinue the interview without affecting their lives or work.

Results.

Establishment of an item pool. Twenty-seven risk factors were extracted from the literature review (**Table 2**). We qualitatively interviewed the ICU healthcare staff using 3 predetermined interview outlines. After each interview, we extracted risk factors identified by the healthcare staff in the interviews as affecting the occurrence of FI. Risk factors that were directly mentioned or implied by the healthcare staff were counted, and the frequency of each item was calculated relative to the total results, which ranged from 4.45% to 86.36% (**Table 3**).

After comprehensively analyzing the results obtained using the aforementioned 2 methods, the group members discussed the risk factors. Ultimately, 23 risk factors were collected in the pool of items. Among these items, age, acute gastrointestinal injury grade (AGI grade),

Table 1 - Pairwise comparison scale of items in the AHP.

Difference	Score	Relative importance	Explanation
0	1	Of equal importance	The items made the same contribution to the goal
1	3	Slightly important	This item was slightly better than the other item based on experience
2	5	Fundamental importance	This item was better than the other item based on the experience
3	7	Really important	This item was much more favorable than other item based on the experience
4	9	Absolutely important	The degree of importance for this item is very obvious
-1,-2,-3,-4	1/3,1/5,1/7,1/9		There is an inverse relationship between these items

Table 2 - Results of literature review.

Authors	Year	Type	Risk factors
Moore et al[31]	2011	Review article	21
Im et al[32]	2014	Original research article	24
Paola Iovino et al[27]	2013	Original research article	3
David et al[28]	2013	Review article	7
Kao et al[33]	1999	Original research article	10
Nguyen et al[34]	2008	Original research article	26
Francisco et al[15]	2012	Original research article	1, 7
Tan et al[3]	2011	Review article	6, 11
Reintam Blaser et al[1]	2012	Review article	5, 9, 23
O'Leary-Kelley et al[35]	2005	Original research article	5, 20, 23
Stewart et al[36]	2014	Review article	5, 8, 19, 23
Camilleri et al[5]	2013	Review article	2, 4, 26, 27
Chapman et al[37]	2013	Review article	1, 2, 8, 10, 27,
Reintam et al[16]	2009	Original research article	1, 2, 4, 6, 20, 22, 26
Mentec et al[17]	2001	Original research article	1, 9, 13, 14, 20, 23, 24, 26
Nguyen et al[4]	2007	Original research article	1, 3, 4, 6, 11, 12, 16, 20
Blumenstein et al[38]	2014	Review article	4, 6, 7, 8, 14, 15, 16, 17, 18, 25,
Btaiche et al[30]	2010	Review article	6, 8, 11, 13, 16, 17, 20, 25, 24, 26

1 - age, 2 - hyperglycemia, 3 - prolonged bedrest (length of stay in the intensive care unit prior to the study), 4 - postoperative 2~3 days, 5 - abdominal distension, 6 - hypoproteinemia, 7 - long-term fasting or total parenteral nutrition, 8 - habitual constipation, 9 - weakened or absent bowel sounds, 10 - spinal cord injury, 11 - traumatic brain injury, 12 - ISS score (multi-system trauma), 13 - hypokalemia, 14 - severe malnutrition, 15 - nutrient solution temperature, 16 - nutrition liquid infusion speed, 17 - concentration of nutrient solution, 18 - nutrient solution pollution, 19 - elevation of the head of the bed, 20 - mechanical ventilation, 21 - mild therapeutic hypothermia, 22 - Acute Physiology and Chronic Health Evaluation II score, 23 - gastric residuals value, 24 - use of antacid agents, 25 - use of broad-spectrum antibiotics, 26 - use of sedative or analgesic agents, 27 - use of narcotic drug

Glasgow Coma Scale score (GCS), Injury Severity Score (ISS), Acute Physiology and Chronic Health Evaluation II score (APACHE II score), blood glucose level, and continuous use of broad-spectrum antibiotics had sub-classification items; the remaining items were included as single items. The items were generally divided into the following categories: 1) general conditions: age, prolonged bed rest, postoperative 3 days, constipation, and abdominal distension; 2) patient conditions: AGI grade, severe infection, traumatic brain injury, ISS score, severe malnutrition, APACHE II score, gastric residuals value (GRV), blood glucose level, albumin (ALB) level, hypokalemia, melena, and spinal cord injury; and 3) treatment measures: elevation of the head of the bed <30°, mechanical ventilation, use of antacid agents, sedative or narcotic agents, or analgesic drugs, and continuous use of broad-spectrum antibiotics.

Expert consensus results. To evaluate the previously described pool of items, we performed 2 rounds of the Delphi technique. At the end of the expert consensus, 30 experts had completed 2 rounds of consultation, of which 20 (66.67%) had senior professional titles and 10 (33.33%) had intermediate grade titles.

The 30 experts had worked in ICUs for a range of 8-36 years, with an average working duration of 18.17 (SD 8.96) years. The recovery rates of the first rounds of expert consensus was 90.91% and second 100%; and the effective rate of both rounds was 100%; of the experts, 80% put forward opinions in the first and 10% in the second rounds. The expert authority coefficient (C) was determined by the experts' judgment basis coefficients (CI, including theory analysis, experience, reference literature, and intuitive sense) and familiar degree coefficients (CS, including very familiar, familiar,

Table 3 - Semi-structured interview results.

Risk factor	Frequency
Nutrient solution temperature	86.36%
Intestinal function	81.82%
Gastric residuals	81.82%
Constipation	72.73%
Nutrient solution volume	68.18%
Nutrient solution type	54.55%
Abdominal distension	50.00%
Nutritional liquid infusion speed	50.00%
Gastrointestinal injury	36.36%
Nutrition solution concentration	36.36%
Bowel sounds	36.36%
Stress	34.81%
Drugs	31.81%
Prolonged bedrest	31.81%
Digestive tract hemorrhage	31.81%
Nutrient solution preservation	27.27%
Age	22.73%
Gut microbiota imbalance	22.73%
Nutritional status	22.73%
Surgery	22.73%
Underlying diseases	18.18%
Long-term total parenteral nutrition	18.18%
Patient condition	18.18%
Turning over the body	13.64%
Pain	4.54%
Hyperglycemia	4.54%

understanding, and unclear). The formula for the expert authority coefficient was:[13] C=(CI+CS)/2. In this study, the expert authority coefficients of the first rounds of Delphi was 0.85 (CI for 0.86, CS for 0.84) and second rounds was 0.92 (CI for 0.93, CS for 0.91). The coordination coefficient for the experts' opinions was evaluated using Kendall's coefficients of concordance (Kendall's W), which was 0.33 (x^2=329.42, p=0.000) for the first and 0.32 (x^2=270.19, p=0.000) for the second rounds.

In the first round, the mean item score was from 2.30 to 4.73, and the coefficients of variation ranged from 0.14 to 0.44 (**Table** 4). Seven items, including age ≥60 years, mild traumatic brain injury (8<GCS≤12), moderate traumatic brain injury (12<GCS≤15), blood glucose level ≥10.0mmol/L, GRV>100 ml, continuous use of broad-spectrum antibiotics ≥3 days, and AGI grade I met the screening criteria with a mean scoreless than 3.0 and a coefficient of variation greater than 0.3. After group discussion, all these items except AGI grade I were removed because this item was a comprehensive evaluation of the gastrointestinal condition.[1] Based on the experts' advice, we removed the items constipation, abdominal distension and melena, GRV >200 ml, and GRV >400 ml due to overlap with the AGI grade, and we deleted APACHE II score ≥15 because it was close to APACHE II score ≥20, which was shown to be a risk factor for FI in our subsequent analysis.[14] We also added 9 items,[1,4,15-18] including gastrointestinal tract disease/injury, acute/severe acute pancreatitis, abdominal surgery, hypoproteinemia, acidosis (pH <7.35), hypoxemia (PaO_2 <60 mmHg), long-term fasting or total parenteral nutrition and AGI III grade, because these items should directly or indirectly affect gastrointestinal functions and an AGI III grade is a worse state compared with AGI I or II grade. Additionally, we changed the item "use of anesthetics within 72 hours" to "use of anesthetics within 24 hours" and the item "severe infection" to "2.4 mmol/L lactic acid ≤4 mmol/L". Gastrointestinal myoelectric activity will reactivate within 24 hours after general anesthesia.[19] Lactic acid is marker for infection, especially in sepsis;[20] however, a lactic acid level exceeding 4.0 mmol/L is an important sign of hemodynamic instability.[21]

In the second Delphi round, all items had mean scores between 3.00 and 4.57, and the coefficients of variation ranged from 0.16 to 0.43 (**Table 5**). Based on the experts' advice and the results of the current round of consultation, we made corresponding adjustments to individual items and removed "ISS score ≥16" for it was close to "ISS score ≥25" according to the experts comments, while the latter implied greater likelihood of FI. We also deleted the "spinal cord injury" because the AIS-90 score table showed that high level or complete spinal cord injury patients had ISS scores as high as 25 points, which was redundant with "ISS score ≥25". Besides, "spinal cord injury" has met the screening criteria with a mean score less than 3.0 and a coefficient of variation greater than 0.3. Additionally, we merged "2.4 mmol/L lactic acid ≤4 mmol/L" and "continuous use of broad-spectrum antibiotics ≥7days" into "sepsis or intestinal infection". However, we changed this item back to the original term because lactic acid did not completely represent the infection level, hemodynamics could also be an important reason for its rise,[20] and broad-spectrum antibiotics were also a consideration for infection. Further, we changed "systemic infection" to "sepsis" according to the third international consensus definitions for sepsis and the guidelines for nutrition

Table 4 - Results of two rounds of expert consensus.

Risk factors	First round		Second round	
	Mean	Coefficient of variation	Mean	Coefficient of variation
Age ≥60 years	2.67	0.33		
Age ≥70 years	3.37	0.33	3.50	0.27
Elevation of the head of the bed <30°	3.57	0.35	3.07	0.33
Prolonged bedrest	3.77	0.31	3.67	0.24
Postoperative 3 days	3.43	0.32	3.40	0.28
Abdominal surgery			4.27	0.21
Long-term fasting or total parenteral nutrition			4.20	0.18
Severe malnutrition	3.67	0.34	3.70	0.23
Spinal cord injury	3.17	0.32	2.97	0.37
ISS score ≥16	3.20	0.22	3.67	0.22
ISS score ≥25	4.23	0.15	4.23	0.17
APACHE II score ≥15	3.13	0.27		
APACHE II score ≥20	4.10	0.23	4.13	0.18
GCS score ≤8	3.83	0.24	3.27	0.32
8<GCS score≤12	2.97	0.30		
12<GCS score ≤15	2.30	0.41		
Severe infection	4.00	0.21		
Blood glucose level ≥10.0mmol/L	2.57	0.42		
Blood glucose level ≥11.0mmol/L	3.07	0.44	3.13	0.23
Hypoproteinemia (ALB <35 g/L)	3.00	0.39	3.03	0.29
Hypokalemia (K^+ <3.5mmol/L)	3.00	0.39	3.17	0.35
GRV >100 ml	2.67	0.40		
GRV >200 ml	3.83	0.24		
GRV >400 ml	4.63	0.17		
Constipation	3.63	0.32		
Melena	3.77	0.32		
Abdominal distension	4.73	0.14		
Acute/severe acute pancreatitis			4.20	0.22
Gastrointestinal tract disease/injury			4.03	0.22
MODS			4.30	0.24
Acidosis (pH <7.35)			3.03	0.43
Hypoxemia (PaO_2 <60 mmHg)			3.67	0.26
2.4 mmol/L ≤Lac ≤4.0 mmol/L			3.07	0.28
AGI grade I	2.80	0.33	3.37	0.26
AGI grade II	4.20	0.22	4.07	0.17
AGI grade III			4.57	0.16
Mechanical ventilation	3.37	0.38	3.17	0.32
Antacid agents	3.00	0.34	3.00	0.21
Sedative and analgesic agents	3.27	0.31	3.10	0.27
Continuous use of broad-spectrum antibiotics ≥7days	3.50	0.39	3.20	0.30
Continuous use of broad-spectrum antibiotics ≥3days	2.60	0.37		
Used of anesthetics within 72 hours	2.90	0.26		
Used of anesthetics within 24 hours			3.10	0.26

ISS - Injury Severity Score, APACHE II - Acute Physiology and Chronic Health Evaluation II score, GCS - Glasgow Coma Scale score, PaO_2 - arterial partial pressure of oxygen, ALB - albumin, MODS - multiple organ dysfunction, GRV - gastric residuals value, AGI grade- acute gastrointestinal injury grade

support therapy in the adult critically ill patient,[22-24] which is more practical to evaluate. We also merged "postoperative 3 days" and "use of anesthetics within 24 hours" into one item ("postoperative one day") aiming at non-abdominal surgery patients ("abdominal surgery" has already been separately listed as an item), whose intestinal function should be inhibited by analgesic agent within 24 hours after operation, while the inhibition will generally decrease beyond 24 hours. This study retained the final 23 items and divided them into the following 5 categories: (1) general conditions: age ≥70 years, prolonged bed rest, postoperative one day, abdominal surgery, long-term fasting or total parenteral nutrition, and elevation of the head of the bed <30°; (2) patient conditions: gastrointestinal tract disease/injury, acute/severe acute pancreatitis, sepsis or intestinal infection, multiple organ dysfunction (MODS), APACHE II score ≥20, severe malnutrition, severe head injury, and ISS score ≥25; (3) biochemical indexes: ALB level <35 g/L, hypoxemia (PaO_2<60 mmHg), pH value <7.35, blood glucose level ≥11.0mmol/L: and K^+ level <3.5 mmol/L; (4) gastrointestinal functions: AGI grade; and (5) treatment measures: mechanical ventilation and use of sedative or analgesic agents and antacid agents.

Weight determination. Based on the final results of the second Delphi round, the AHP was used to test the consistency of the questionnaire and to calculate the item weights. According to the consistency test results, one of the 30 questionnaires had a CR value of >0.1, which did not pass the test, and therefore, it was excluded. Finally, 29 questionnaires were included, and the average normalized weights (Wi) of each item were used to determine the weights of the items (**Table 5**).

Table 5 - Feeding intolerance risk factor items and weights.

Article	Risk assessment items	Weighted arithmetic mean	Weight
General conditions (total weight 23)	Abdominal surgery	0.0569	6
	Long-term fasting or total parenteral nutrition	0.0521	5
	Prolonged bedrest	0.0376	4
	Age ≥70 years	0.0348	3
	Postoperative 1 day	0.0303	3
	Elevation of the head of the bed <30°	0.0245	2
Patient conditions (total weight 42)	ISS score ≥25	0.0846	8
	Acute/severe acute pancreatitis	0.0569	6
	MODS	0.0628	6
	Gastrointestinal tract disease/injury	0.0486	5
	Sepsis or intestinal infection	0.0514	5
	APACHE II score ≥20	0.0483	5
	Severe malnutrition	0.0362	4
	GCS score ≤8	0.0272	3
Biochemical indexes (total weight 14)	Hypoxemia (PaO_2 <60 mmHg)	0.0355	4
	Acidosis (pH <7.35)	0.0266	3
	Hypokalemia(K^+ <3.5 mmol/L)	0.0266	3
	Hypoproteinemia (ALB <35 g/L)	0.0210	2
	Blood glucose level ≥11.0 mmol/L	0.0221	2
Gastrointestinal functions (total weight 15)	AGI grade III	0.0707	7
	AGI grade II	0.0479	5
	AGI grade I	0.0269	3
Treatment measures (total weight 6)	Mechanical ventilation	0.0245	2
	Sedative or analgesic agents	0.0207	2
	Antacid agents	0.0200	2

APACHE II - Acute Physiology and Chronic Health Evaluation II score, GCS - Glasgow Coma Scale score, PaO_2 - arterial partial pressure of oxygen, ALB - albumin, AGI grade- acute gastrointestinal injury grade, MODS - multiple organ dysfunction

Discussion. Feeding intolerance is a combined result of many different factors, and drastic changes in neurohumoral regulation, energy metabolism and the internal environment are important basis for FI in critically ill patients. In vivo changes in stress-induced adrenaline and glucocorticoid hormone changes through activation of the coeruleus and the sympathetic adrenal medulla and hypothalamic pituitary adrenal cortex systems may lead to gastrointestinal mucosa synthesis and inhibited secretion or severe contraction of the abdominal organs and blood vessels.[25,26] Moreover, a continuous high decomposition status within the body may lead to a negative nitrogen balance, which can damage immune functions and even lead to multiple organ dysfunction. The semi-structured interviews showed that the healthcare staff knew a few risk factors causing FI in critically ill patients, and most of the results were consistent with the results of the literature review. However, we also found that the healthcare staff did not know the connotations of how to use some of the risk factors, such as the APACHE II or ISS score and the drug types (including sedatives, analgesic, and narcotics), to assess the patient's condition. Additionally, some differences in the understanding of the risk factors may exist between different healthcare staff, such as underlying diseases, intestinal flora imbalances, and other risk factors. Therefore, the identification of items based on the literature analysis and the semi-structured interviews may comprehensively cover the risk factors, which should make it easier for the healthcare staff to screen the risk factors. During the Delphi expert consultation rounds, the experts provided substantial professional guidance and recommendations for the study. In the first round, 26 relevant recommendations were contributed; these recommendations corrected existing problems in the study, such as unclear items and redundancy, and effectively compensated for any deficiencies during the early stages of the establishment of the item pool. Additionally, we clarified the classification of each item according to the experts' opinions. Beyond the original 3 dimensions ("general conditions", "patient conditions", and "treatment measures"), we added 2 dimensions for "gastrointestinal functions" and "biochemical indicators", which made the classification of risk factors clearer and more reasonable. The experts selected to participate in the 2 Delphi rounds were chosen from a wide range of geographical areas and had a high level of relevant professional knowledge that laid the foundation for the reliability of the study results. Therefore, the items ultimately identified as risk factors for FI meet the requirements for test items in clinical scales and relevant for using in further studies.

To clarify the weight of each risk factor, we determined the relative importance of each item based on the Delphi method results and assigned ratings; additionally, we utilized the AHP to calculate the weights of the risk factors and avoid problems associated with the experts' subjective opinions and difficulties in determining logical relationships among an excessive number of items. Of the 5 dimensions, patient conditions had the highest weight (42%); and items that reflected the severity of the patients' conditions, such as severe acute pancreatitis, MODS, the APACHE II score, and the ISS score, had especially high weight values. The results of this study showed that 3 indicators related to the AGI grade accounted for 15% of the total weight, which clearly showed that gastrointestinal disease or injury was an important risk factor for inducing FI. Additionally, general conditions (23%) and biochemical indicators (14%) of the total weight, most likely because patients with long-term fasting or total parenteral nutrition or prolonged bedrest were more prone to slow intestinal peristalsis, gastrointestinal mucosal atrophy, thinned or broken villi, and ultimately digestion and absorption barrier dysfunction.[27-29] When accompanied by hypoproteinemia, acidosis, and biochemical disorders, these conditions may facilitate the development of gastrointestinal edema or paralysis,[3,18] Additionally, the receipt of some treatment measures (constituting 6% of the total weight), such as sedative and analgesic agents, that act on relevant receptors in the gastrointestinal tract and reduce gastrointestinal excitatory neurotransmitter release may directly or indirectly inhibit gastrointestinal functions, ultimately inducing FI.[7,30] Hence, FI occurrence is the result of complex systemic pathophysiological responses in critically ill patients and requires a comprehensive analysis of significant and subtle risk factors to enable reasonable risk assessment by the healthcare staff.

Therefore, the determination of the FI risk factor items and their weights may help clinical healthcare staff assess FI risk factors in critically ill patients in a focused and systematic manner, avoid the omission of important risk factors due to different levels of professional knowledge and work experience, lay the foundation for the development of a clinical test scale, and provide a reference for the implementation of effective measures to prevent FI in critically ill patients.

Study limitations. The first part of the study is based on the literature, all the further steps are complicated assessment of subjective evaluation and interpretation. Although they may help to identify broader consensus, it is still subjective interpretation. Therefore, further clinical study is necessary to test the validity of the terms.

In conclusion, feeding intolerance is an important factor that affects the clinical malnutrition and clinical outcome of critically ill patients who receive enteral nutrition. This study identified risk factors that affected the occurrence of feeding intolerance, and these factors were categorized into 5 dimensions (general conditions, patient conditions, biochemical indexes, gastrointestinal functions, and treatment measures). The selected items might help clinical healthcare staff clarify risk factors and laid the foundation for the future development of a scale.

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