The effect of dietary fiber on gut barrier function, gut microbiota, short-chain fatty acids, inflammation and clinical outcomes in critically ill patients: A systematic review and meta-analysis

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Conflict of interest

We declare that we have no conflict of interest.

Abstract

Background: Although some studies have explored the relationships between dietary fiber (DF) supplement and gut barrier function, changes of gut microbiota and other clinical outcomes in critically ill patients, the results from different studies were not consistent.

Objective: The purpose of this study was to explore the effect of dietary fiber on gut barrier function, gut microbiota, short-chain fatty acids (SCFAs), inflammation and clinical outcomes in critically ill patients.

Methods: A search was performed through PubMed, Embase, the Cochrane Central Register of Clinical Trials, Web of Science and EBSCO-host that includes Health Sciences Research from inception to July 12, 2021. Data were pooled using fixed effects model for low heterogeneity and random effects model for high heterogeneity. Data were expressed as mean difference (MD) or odds ratio (OR) with confidence interval.

Results: A total of 21 studies involving 2084 critically ill patients were included. The results showed that there was a significant reduction in intestinal permeability demonstrated by lactulose/rhamnose ratio (MD:-0.04; 95%CI:-0.08, -0.00; P=0.03) on day 8 in DF supplement group. Three studies reported the relative abundance (RA) of gut microbiota and the results showed the RA of some SCFAs producers increased higher in DF supplement group. There was a significant decrease in C-reactive protein on day 14 (MD:-36.66; 95%CI:-44.40, -28.93; P<0.001) and the duration of hospital stay (MD:-3.16; 95%CI:-5.82, -0.49; P<0.05)

after DF supplement. There were no significant differences on SCFAs levels, the duration of mechanical ventilation and mortality between the two groups. However, in subgroup analysis, the results indicated there was a significant reduction on the duration of mechanical ventilation in fiber combined probiotic group (MD:-13; 95%CI:-19.69, -6.31; P<0.001). Besides, significant decreases in the duration of hospital stay and risk of mortality were seen in the subgroups with fiber supplementary dose ≥20 g/d (MD:-5.62; 95%CI: -8.04, -3.21; P<0.0001; OR: 0.18, 95%CI: 0.06, 0.57, P=0.004), as well as in medical ICU (MD:-4.77; 95%CI: -7.48, -2.07; P<0.01; OR: 0.13; 95%CI: 0.03, 0.65; P<0.05).

Conclusions: Dietary fiber may improve the gut barrier function, modulate the intestinal microbiota, decrease systemic inflammatory response and may advance the clinical outcomes in critically ill patients.

Key words: Dietary fiber, Gut barrier function, Gut microbiota, Inflammation, Clinical outcomes, Critically ill patients

Clinical relevancy statement

Dietary fiber may improve gut barrier function and inflammation, increase relative abundance of some short-chain fatty acids in patients that are critically ill. Besides, fiber supplementary dose ≥20 g/d may improve the clinical outcomes of ICU patients. Hence, if the patients could tolerate dietary fiber, it is necessary for ICU patients to supply sufficient dose of DF.

Introduction

Critically illness can lead to derangement of gut epithelial mucus layer and increased gut permeability[1]. This may increase the chances of luminal microorganisms and endotoxin to reach distant extra-intestinal sites[2]. This can result in poorly controlled systemic inflammatory response[1, 3], acute respiratory distress syndrome (ARDS), renal failure, prolonged mechanical ventilation and intensive care unit (ICU) stay, and even increased risk of mortality[4, 5]. About 50% of critically ill patients experience gut barrier dysfunction[4]. A study showed that gut microbiota provide energy for the gut epithelium to maintain the mechanical barrier's integrity and continuity of gut epithelial lining by fermenting carbohydrates and indigestible oligosaccharides[6, 7]. Therefore, adequate and reasonable dietary ingredient has become an important factor in maintaining the intestinal barrier function[8, 9].

Dietary fiber (DF) is a class of dietary polysaccharides that are neither digested nor absorbed in the human small intestine[10]. As an important substrate to the community of microorganisms that inhabits the distal gut, DF is depolymerized and fermented into host-absorbable short-chain fatty acids (SCFAs) in the colon[11] and provides energy for microbiota and gut epithelium. Dietary fiber deprivation, together with a fiber-deprived related mucus-eroding microbiota such as *clostridia*, promotes greater epithelial access by the mucosal pathogen, leading to gut barrier function impairment[12, 13]. Johansson et al. found that if DF is deprived, modified gut microbiota will use an alternative energy source, the glycoprotein-rich mucus layer that covers the gut epithelium as a first line of immune defense[14], leading to thinner colonic mucus [15], impaired gut mucosal barrier and increased permeability. On the other hand, there have been studies exploring the effect of DF supplementation on improvement of gut barrier function, change of gut microbiota and SCFAs, and other clinical outcomes in critically ill patients. But, the results from these different studies are not consistent. Furthermore, it is uncertain whether ICU patients who receive broad-spectrum antibiotics, mechanical ventilation, and other interventions will

respond to dietary fiber in the same manner as other ambulatory patients. Hence, the purpose of this study was to explore the effect of dietary fiber on gut barrier function, gut microbiota, SCFAs, inflammation and clinical outcomes in critically ill patients.

Methods

Search strategy

This meta-analysis was conducted in line with the guidelines of Cochrane Handbook for Systematic Reviews of Intervention and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[16]. A literature review was performed using electronic databases including PubMed, Embase, the Cochrane Central Register of Clinical Trials, Web of Science and EBSCO-host that encompasses Health Sciences Research (including MEDLINE, Academic Search Ultimate, APA PsycNet and CLNAHL) from inception to July 12, 2021. The search strategy also involved the use of keywords and Medical Subject Headings of the National Library of Medicine. There was no restriction on language.The strategies and the search terms used are outlined in Table S1.

Study Selection

Studies were selected based on an initial screen of identified abstracts or titles and a second screen of full-text articles. Analysis of the reference lists of retrieved articles and relevant systematic reviews were conducted. The inclusion criteria for the study were as following: (a) randomized controlled trial (RCT) or cohort study;(b) participants were critically ill patients; (c) with dietary fiber intervention; (d) reported at least one of results of short-chain fatty acid, gut microbiota, gut barrier function, systemic inflammatory response (C-reactive protein, CRP; proinflammatory, PCT; interleukin-6, IL-6; tumor necrosis factor-α, TNF-α; malondialdehyde, MDA) or clinical outcomes (the duration of mechanical ventilation or hospital stay or ICU mortality). Exclusion criteria were as follows: (a) animal studies; (b) participants aged < 18 years; (c) systematic reviews, reviews, opinion papers, case study and conference abstract.

Data Extraction and Quality Assessment

Two investigators independently extracted the data from eligible studies based on title, abstract, and full text. Disagreements were resolved by a third investigator. The following data were extracted from included studies: author's name, year of publication, country, study design, participant characteristics, sample size, intervention details (the type of dietary fiber and dose), treatment duration, mean value and standard deviation (SD) of the duration of mechanical ventilation and hospital stay, the SCFAs levels and the relative abundance of gut microbiota. If the study only reported the median and quartile range, data were converted to mean and SD[17].

The quality of cohort study was assessed using Newcastle-Ottawa scale (NOS)[18]. There were three dimensions in the NOS: selection, comparability, and outcomes or exposure. The NOS assigns a maximum of 4 points for selection, 2 for comparability, and 3 for outcomes or exposure. A score above 6 was considered as high quality, while below 6 was low quality. The quality of RCT study was assessed using the Jadad scale[19]. There were three dimensions in Jadad scale: study design, blinding, and loss of participants to follow-up. Points were assigned to reviewed studies as follows: 2 points if the study was properly randomized, 2 points when blinding was done correctly, and 1 point when the authors reported withdrawals and dropouts. The studies were scored using a range of 0 to 5 (where 0 is the weakest and 5 is the strongest). A score below 2 indicated low quality.

Statistical Analysis

The meta-analysis was performed by RevMan 5.3 (http:// tech.cochrane.Org/ revman /download). Data were combined to estimate the pooled odds ratio (*OR*) with 95% confidence intervals (*CI*) for gastrointestinal symptom and ICU mortality. The mean difference (*MD*) was used to calculate effect sizes for outcomes with continuous variables and with the same unit of measurements. A heterogeneity test among studies were evaluated with I^2 statistics (25%, 50%, and 75% correlate with low, moderate, and high heterogeneity, respectively) for

each outcome[20]. If there had been no statistical heterogeneity, we would have used a fixed-effect model. Instead, we chose a random-effect model. Subgroup analysis were performed to verify the factors that may affect the effect of DF on effect of clinical outcomes, including the type of DF, fiber supplement dose, intervention time and the type of ICU. Publication bias was evaluated by funnel plot. Asymmetry in funnel plots indicated publication bias in meta-analysis. A two-sided *P*-value of less than 0.05 was considered significant[21].

Results

Study Selection

A total of 4051 articles were identified in the literature search. After removing duplicate articles, 2961 articles were left for further review. There were 2855 articles excluded by reading title and abstract and 106 articles were left for more details. After review, 82 articles were excluded for the reasons shown in Figure 1. Finally, there were 20 articles included in our study[3, 22-40].

Study Characteristics

There were 20 RCT studies[22-40] and 1 cohort study[3]. Table 1 presents a summary of study characteristics for the included studies. The total of 21 studies included 2084 critically ill patients. The publication year ranged from 2000 to 2021. Eleven studies[24, 28-32, 34-36, 38, 39] were from Europe, four[3, 25, 27, 37] were from America and six[8, 22, 23, 26, 33, 40] were from Asia. The types of dietary fiber were fiber[3,8,22-24,26,27,29,30,33,37-40], probiotic[25,28,31,34-36], and fiber combined probiotics[32].The DF supplement dose ＜20g and ≥20g were 13 studies[22,24,27,28,30-35,37,39,40] and 8 studies[3,8,23,25,26,29,36,38], respectively. Eleven studies did not report the results of adverse outcomes of DF supplement[23-26,28,30,31,34-36,39] and 6 studies shown there was no significant difference in adverse outcomes between DF group and fiber-free group[3,22,27,29,33,40]. Besides, four studies indicated the rates of adverse outcomes were significantly reduced in DF group[8,32,37,38]. The duration of the intervention ranged from 3-30 days. Twenty studies had high methodological quality (Table 1).

Effect of Dietary Fiber on Intestinal Permeability

Three studies[23, 28, 34] reported the results of lactulose/rhamnose (L/R) permeability tests. Figure 2 showed that there was no significant difference in L/R ratio between the fiber supplement group and fiber free group on day 1 (MD:-0.03; 95%CI:-0.07, 0.01; P=0.17; I^2=36%). However, on day 8, there was a significant reduction in L/R ratio with fiber supplement group (MD:-0.04; 95%CI:-0.08, -0.00; P=0.03; I^2=0%). The heterogeneity among studies on day 1 and day 8 were moderate and low, respectively.

Effect of Dietary Fiber on SCFAs Levels

SCFAs levels was measured in 2 articles involving 42 patients[27, 33]. The meta-analysis showed that there was no significant difference between the fiber supplement group and fiber free group (MD: 162.29; 95%CI: -18.82, 343.41; P=0.08; I^2=0%). The heterogeneity of SCFAs levels was low. Figure S1.

Effect of Dietary Fiber on Gut Microbiota

There were 3 studies that showed the results of the relative abundance of gut microbiota[3, 27, 33]. All of the studies reported the results of SCFAs-producing bacteria. Freedberg et al.[27] indicated that there was no significant difference in the relative abundance of SCFAs producers' between the fiber supplement group and no fiber group from baseline to day 3 (median:+61%; IQR:-51 - +1688 *vs* median:-46%; IQR:-78 - +13; P=0.28). However, when SCFAs-producing operational taxonomic units were considered, the difference in SCFAs producers seen with the fiber group became statistically significant (P< 0.01). Among the SCFAs producers, the greatest changes with fiber supplement group were seen corresponding to *Faecalibacterium and Odoribacter* (fiber supplement group *vs* no fiber group: +0.72 vs -0.44 and +0.35 vs -0.14).

Fu Y et al.[3] pointed that there was a significant difference about increased SCFAs producers' relative abundance between the fiber supplement group and no fiber group from

baseline to day 3 (median:2.8%; IQR:0.42% - 7.9% *vs* median:0.08%; IQR:0.062% - 6.3%; *P* = 0.02). Besides, a higher change with fiber supplement group was seen in the relative abundance of *Odoribacter* (high fiber vs no fiber: median:1.8% *vs* 0.4%). The SCFAs producers *Blautia* (4-fold difference) and *F. prausnitzii* (3.9-fold difference) were among 7 taxa that were enriched in the high-fiber group compared with the no-fiber group by using an untargeted algorithm to test the differences in relative abundance across all bacterial taxa based on fiber intake. Moreover, *Enterococcus* (4.8-fold difference) was the only taxon that was enriched in the no fiber group compared with the high-fiber group. Higher fiber intake was associated with lower abundance of *Enterococcus* after 72 hours (median 0.066% high fiber vs 0.30% no fiber). This study also found that higher fiber intake was associated with higher fecal microbial diversity at 72 hours ($P = 0.04$).

Majid et al.[33] showed that there were no significant differences in any of gut microbiota at baseline, but there were significantly lower concentrations of *F. prausnitzii* (P=0.01) and *Bacteroides-Prevotella* ($P = 0.05$) at 7 days after intervention in the oligofructose/inulin group compared with placebo group.

Effect of Dietary Fiber on Systemic Inflammatory Response

There were 3 studies that reported the results on CRP on day 1[29, 39, 40] and 2 studies on day 14[39, 40]. The results of day 1 and day 14 involved 134 and 104 patients respectively. There was no significant difference of the CRP on day 1 (MD:0.10; 95%CI:-6.95, 7.14; P = 0.98; $I^2 = 0\%$), while a significant reduction on day 14 (MD:-36.66; 95%CI: -44.40, -28.93; P < 0.01; $I^2 = 0\%$) were observed in the fiber supplement group. The heterogeneity of the CRP on day 1 and day 14 was low (Figure 3.)

Kotzampassi et al.[32] pointed that there were no significant increases on day 4 for the inflammatory markers of PCT, IL-6, TNF- α and MDA, while there were greater reductions on day 7 for the above inflammatory parameters in the fiber supplement group. Alenka et al.[23] demonstrated that the level of PCT in fiber supplement group significantly decreased compared with the fiber free group after intervention (0.50±1.26 *vs* 1.25 ±0.98; $P = 0.024$).

Mcnaught et al.[34] indicated that there were no significant differences in IL-6 on day 1 and was significantly lower at day 15 ($P = 0.04$) in fiber supplement group. However, Chen et al.[8] demonstrated there was no significant difference in IL-6 on day 1 and day 7 between DF group and fiber-free group ($P > 0.05$).

Effect of Dietary Fiber on Clinical Outcomes

Effect of Dietary Fiber on the Duration of Mechanical Ventilation

The number of studies that measured the duration of mechanical ventilation was 6 involving 1113 patients[23, 25, 26, 30, 32, 41]. The pooled effect of dietary fiber on the duration of mechanical ventilation showed that there was no significant difference between the two groups (MD:0.41; 95%CI:-1.89, 2.72; P=0.73; I^2=83%). The heterogeneity among studies was high. The results of subgroup analysis showed that the type of supplement, fiber supplement dose and intervention time were influential factors of the duration of mechanical ventilation. Subgroup analysis demonstrated that fiber combined probiotic intervention led to a significant decrease in the duration of mechanical ventilation (MD:-13; 95%CI:-19.69, -6.31; P=0.0001) compared with fiber-free group. Besides, fiber supplementary dose ≥ 20 g/d (MD:2.10; 95%CI: 0.90, 3.30; $P < 0.001$; $I^2 = 13\%$) and the intervention time ≤ 7d (MD:2.10; 95%CI: 0.90, 3.30; $P < 0.001$; $I^2 = 13\%$) showed that there was significant increase in the duration of mechanical ventilation compared with fiber-free group (Table 2,Figure S2).

Effect of Dietary Fiber on the Duration of Hospital Stay

There were 9 studies involving 1418 patients that reported on the duration of hospital stay[8, 22, 24, 26, 28-30,35, 37]. The results showed that there was a significant decrease on the duration of hospital stay between the two groups (MD:-3.16; 95%CI: -5.82, -0.49; $P = 0.02$; $I^2 = 53\%$). The heterogeneity among studies was high. The results of subgroup analysis pointed that fiber supplementary dose ≥ 20 g/d significantly decreased the duration of hospital stay compared with fiber-free group (MD: -6.26; 95%CI: -9.27, -3.24; $P < 0.0001$; $I^2 = 0\%$). Besides, there was a significant reduction on the duration of hospital stay in medical ICU (MD:-5.00; 95%CI: -8.65, -1.35; $P = 0.007$) and Probiotic supplement (MD:-3.12;

95%CI: -6.18, -0.07; P = 0.04) compared with fiber-free group (Table 3, Figure S3). There were no significant effect found in intervention time. The results of the subgroup analysis are given in Table 3 and Figure S3..

Effect of Dietary Fiber on ICU Mortality

There were 12 studies that reported the results on ICU mortality[22, 24, 25, 28-32, 34-36, 38]. The results indicated that there was no significant difference in ICU mortality (MD:0.87; 95%CI: 0.68, 1.11; P = 0.28; I^2 = 8%) between the two groups. The heterogeneity among studies was low. Subgroup analysis showed that the dose of fiber supplement and type of ICU were the influencing factors of ICU mortality. The subgroup of fiber supplementary dose ≥ 20 g/d (OR: 0.18; 95%CI: 0.06, 0.57; P=0.004; I^2=0%) and medical ICU (OR: 0.13; 95%CI: 0.03, 0.65, P=0.01; I^2=0%) significantly decreased ICU mortality compared with fiber-free group.(Table 4, Figure S4). The funnel plot showed asymmetry, meaning a publication bias in ICU mortality (Figure S5).

Discussion

The results of this meta-analysis and systematic review have shown that dietary fiber may be effective in improving the impaired intestinal permeability ($p < 0.05$) in ICU patients. Moreover, dietary fiber may be effective in increasing the relative abundance of the SCFA producers-*Faecalibacterium*[27], *Odoribacter*[3, 27], *Blautia*[3] and *F. prausnitzii*[3] and in decreasing the level of *Enterococcus*[3], a multidrug-resistant organism. Besides, there was an increased trend of SCFAs level in fiber supplement group of ICU patients. Thus, dietary fiber may improve the gut microbiome of critically ill patients. Dietary fiber intake may significantly reduce CRP on day 14 after intervention[39,40]. At the same time, there were a significant reduction in the durations of hospital stay[8, 22, 24, 26, 28, 29, 30, 35, 37] and the duration of mechanical ventilation[23, 25, 26, 30, 32, 35] and the ICU mortality[22, 24, 25, 28,29, 30,31, 32,34, 35, 36, 38] in some subgroups in the fiber supplement group (P< 0.05). Cara et al[9] conducted a systematic review and meta analysis to explore the safety of using enteral nutrition (EN) formulations containing dietary fiber in ICU patients. The study resulted that EN formulas with fiber may

help reduce incidence and severity of diarrhea and gastrointestinal complications overall in critically ill patients, without increased risk of other adverse events. Consistent with our research, Cara et al[9] reported there was no significance in ICU mortality between DF group and fiber-free group. However, the subgroup of this study showed that the dose of fiber supplement and type of ICU were the influencing factors of ICU mortality.

Intestinal barrier function depends on a stratified system of primary defense[8]. Anaerobic organisms which colonize the mucosal surfaces of the gut, limit overgrowth of other potentially invasive microbes[42]. However, in patients with critically illness and taking limited fiber, the colonic gut commonly becomes colonized by potentially pathogenic facultative bacteria which take the host-secreted mucus glycoproteins located in the mucus layer instead of fiber as a nutrient source[12], resulting in thinner colonic mucosa and dysfunction of mucosal adherence and intestinal permeability. However, the supplemented fiber serves as substrate for gut microbes and provides energy for intestinal wall[12], thus keeping the mucus glycoproteins on gut mucosal surfaces and maintaining the integrity of the intestinal wall. As inferred above, in this study, the lactulose/rhamnose ratio, an indicator of intestinal permeability, statistically decreased in the fiber supplement group on the 8th day of admission in the critically ill patients as compared with the control group, indicating that the one-week dietary fiber intervention effectively improved the high leakage state of the intestinal wall, thereby improving the intestinal barrier function of ICU patients.

There were approximately one-third of ICU patients having gut colonization with multidrug-resistant organisms (MDROs)[27] which is associated with an increased risk for subsequent infection and high-mortality[43, 44]. Knight et al.[45] found that the *Lactobacillus* flora disappeared after 6 to 8 hours of admission among the majority of ICU patients and is replaced by an overgrowth of potentially pathogenic microorganisms. A dysfunction of commensal gut microbiota facilitates colonization with MDROs. Nonpathogenic colonic microbiota in some cases directly antagonize MDROs by producing antibacterial small molecules[46]. Furthermore, SCFAs produced by some commensal microbiota following fiber fermentation are small molecules that have attracted attention in recent years. They confer

protection against MDRO colonization in animal models[47]. Supplement of fiber, either raises the abundance of SCFAs-producing bacteria or increases the SCFAs levels, and confers similar protective effects[48-50]. Freedberg et al.[27] reported that enteral fiber, with a dose of approximately 10 g/d for three days in ICU patients receiving broad-spectrum antibiotics, was associated with trends toward increasing both the relative abundance of SCFAs-producing bacteria and the level of SCFAs. Majid et al.[33] found a dose of 7 g/d of additional oligofructose / inulin for at least 7 days of intervention did lower concentrations of *F. prausnitzii* and *Bacteroides-Prevotella,* although the relative abundance of *bifidobacteria* did not increase in critically ill patients. The result of study by Fu et al.[3] indicated that a higher fiber with a median dose of 13.4 g over 3 days was associated with more SCFAs-producing bacteria in critically ill patients. However, the meta-analysis for two studies showed only a trend of increased SCFAs ($P = 0.08$). The inconsistency of results may be due to the inconsistent dose of DF, because substances have dose-effect relationship. Thus, whether supplement of DF can effectively regulate SCFAs-producers and raise the levels of SCFAs needs to be verified by further high-quality studies.

The CRP is an acute phase reactant, as a response to Interleukin 6 (IL-6) which can be detected in several types of inflammation and also in bacterial infection and it is a measure that helps in diagnosis of bacterial infection [32]. Although one study conducted in the mixed ICU found that, CRP level measured at discharge was not a predictor of readmission or death[29], other studies showed that CRP concentration in plasma is significantly correlated with mortality predictor in the ICU, especially in patients diagnosed with sepsis[51, 52]. The predictive value (AUC) of CRP at admission for mortality was 0.576 in critically ill patients [53]. In this study, we found that the maximum level of CRP concentration in plasma on the 14th day of admission in the group with fiber supplement was significantly lower than that in the group of non-fiber supplement, indirectly indicating that fiber supplement can reduce the inflammation status which may be beneficial in improving mortality in critically ill patients.

Mechanical ventilation is a life-saving method of managing critically ill patients. While prolonged mechanical ventilation would lead to some complications such as ventilator-

induced diaphragm dysfunction[54], we found that a regimen of integrated fiber combined with prebiotics exerted beneficial effect in shortening the duration of ventilatory support. Prebiotics are nondigestible sugars that selectively stimulate the growth of certain colonic bacteria and may stimulate the activity of the hosts endogenous bacteria when administered [32], which is consistent with what we found in this study. At variance with our expect, the results showed a dose of ≥ 20g/d fiber supplement increased duration of mechanical ventilation compared with fiber-free group. We explored the reason that might be associated with a higher APACHE II score in fiber-supplement dose ≥ 20g/d group. Matic et al.[55] found that APACHE II score could predict the duration of mechanical ventilation and higher APACHE II score was associated with a prolonged mechanical ventilation.

The benefits of DF supplementation in ICU patients may shorten the length of the duration of hospital stay and decrease ICU mortality. In this study, It was found that a dose of ≥ 20g/d fiber supplement may improve the length of the duration of hospital stay and the ICU mortality only in patients with medical critically ill patients. Brain injury patients, most of them consisting of surgical critically ill patients, frequently had longer stays in the ICU due to the severity of the brain injury itself, as well as the presence of infectious complications and acute malnutrition [56].

Limitations

The present study had several limitations. First, there were only 3 studies that reported the results of L/R ratio and 2 studies reported the level of CRP on day 14, which may limit the broader application of the results. More high-quality studies are needed in this area of research. Second, there were high heterogeneities in the results of the duration of mechanical ventilation, and hospital stay. Third, the results of the duration of hospital were not adequately adjusted for death. Besides, there were publication bias in all outcomes. Hence, large high quality RCTs focused on dietary fiber are needed to explore the effect of DF on the improvement of gut barrier to ICU patients.

Conclusion

In summary, this study has demonstrated that the dietary fiber may improve the gut barrier function by modulating the intestinal microbiota, decrease systemic inflammatory response and may advance the clinical outcomes in critically ill patients. To better determine the effect and safety of dietary fiber to ICU patients, large high quality RCTs focused on dietary fiber are needed.

Authors' contributions

Ting Liu was major contributor in data extraction, data analysis and writing the manuscript. Can Wang performed systemic reviews and data extraction. Yu-yu Wang, Li-li Wang analyzed data and Xiao-song Jiang did data extraction and quality assessment. Omorogieva Ojo revised and checked manuscript. Xiao-Hua Wang were responsible for article's guidance and revision. All authors read and approved the final manuscript.

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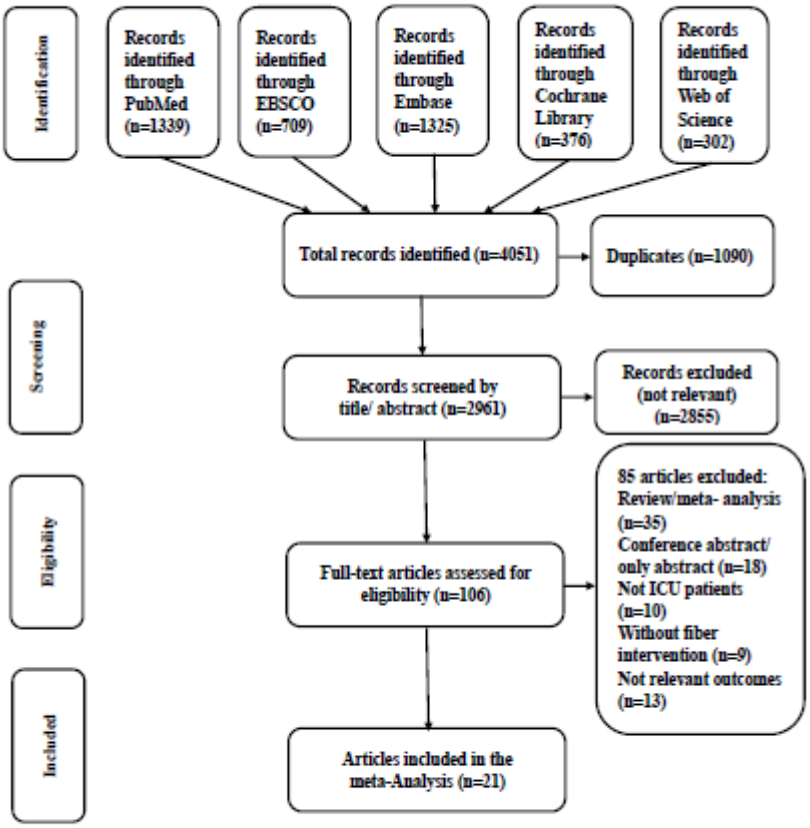

Figure 1.Study Flow Chart of Meta-Analysis

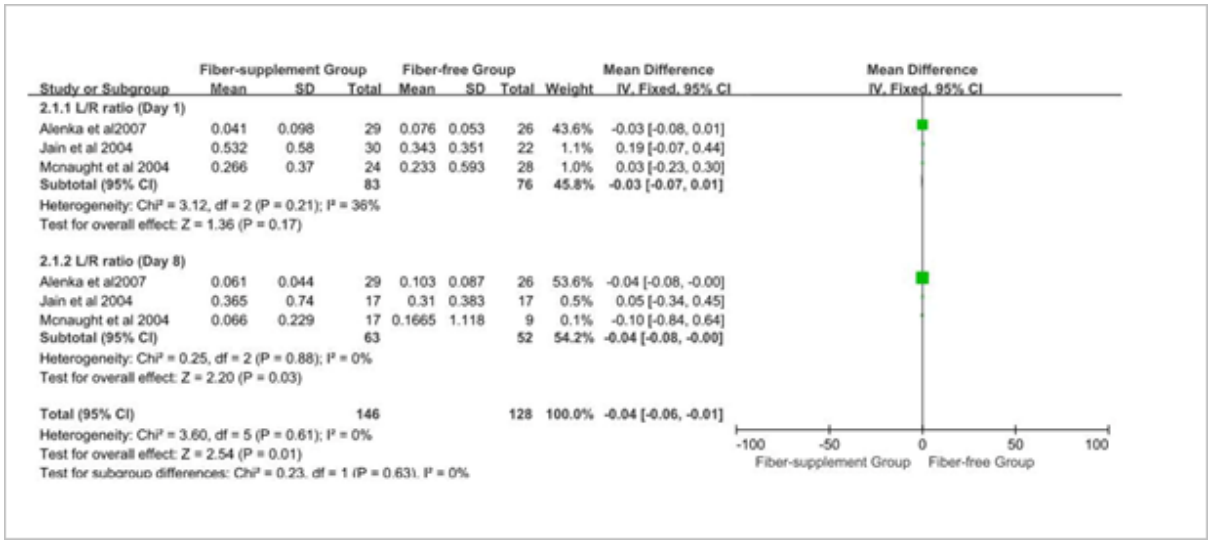

Figure 2. Forest Plot of Effect of Dietary Fiber on Intestinal Permeability

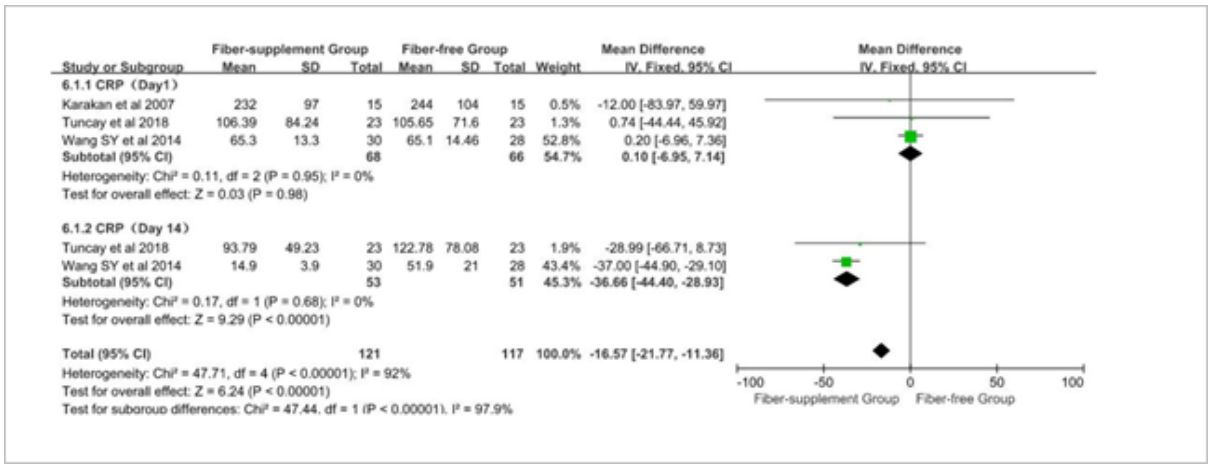

Figure 3. Forest Plot of Effect of Dietary Fiber on CRP

Table 1.Characteristics of study included in Meta-analysis

Study	Country	Study design	Population (Treatment/ Control)	Intervention	Dose of DF	Duration	Median age (years. Treatment/ Control)	APACHE II (Mean ± SD; n; Treatment/ Control)	Outcomes	Jadad/ NOS
Chen T et al.[8]	China	RCT	ICU patients with AP (24/22)	DF:standard formula+20g/d polydextrose Control :standard formula	DF: 20g/d	21d	45.0 ± 9.07) / 51.1 ±12.0	18.5 ±7.71 / 18.6 ±5.65	Systemic Inflammatory Response; Clinical outcomes (the duration of hospital stay)	5
Freedberg, et al.[27] 2020	American	RCT	ICU patients (10/10)	DF: enteral nutrition with	DF: 10.7g/d	30d	< 50 yr.4/3 50–70 yr.4/3 > 70 yr. 2/4	/	The level of SCFAs;	3

				mixed soy- and oat-derived fiber (Promote 1.0 fiber with Abbott Nutrition Chicago 14.3 g fiber/L) Control: Fiber (Promote 1.0)					SCFAs-producers	
Fu Y, et al.[3] 2020	American	Cohort study	ICU patients (36/93)	The calculated patients' total fiber intake was analyzed in	DF:27.3g/d	3d	<60 yr.33/17 60–70 yr. 37/10 >70 yr. 23/12	/	The level of SCFAs; SCFAs-producers; gut micro	8

				tertiles or as a continuous measure					biota	
Tuncay et al. [39] 2018	Turkey	RCT	Neurocritical critical patients (23/23)	DF: used Jevity®, contained 5.3g fiber/ 535 kcal Control: Osmolite® without fiber	DF:5.3g /535 kcal	21d	73.9 ± 15.3/71.8 ± 20.0	<10 score 3/4 ≥10 score 20/19	CRP	3
Fengchan et al. [26] 2017	China	RCT	ICU patients (62/63)	DF: standard formula+24 g pectin Control: standard form	DF:24g/d	7d	48.7±10.7/ 48.2±13.7	12.3± 2.7/12.0±2.3	Clinical outcomes (the duration of mechanical ventilation, hospital	3

				ula					stay and mortality)	
Wang SY et al. [40] 2014	China	RCT	ICU patients (30/28)	DF: standard formula + fiber 3.0 g/1000kcal Control: standard formula	DF:3.0 g /1000kcal	14d	40.1±8.1/41.5±8.7	/	CRP	3
Majid et al. [33] 2013	Malaysia	RCT	ICU patients (12/10）	DF: standard EN treatment +7 g/d of oligofructose/inulin Control: standard EN treat	DF:7g/d	14d	70.6 ±8.9/71.2±10.6	/	The level of SCFAs; gut microbiota	3

				ment						
Plaudis et al. [36] 2012	Latvia	RCT	ICU patients with AP (Synbio group:30 /Fiber group:28 /Control:32)	Synbio Group: low volume enteral feeding + Symbiotic 2000 Forte DF: low volume enteral feeding +33 g fiber Control: low volume enteral feeding	DF:33g/d	21d	/	Synbio group: 8.8±3.6 DF: 8.6±4.9 Control: 6.8±4.3	Clinical outcomes (mortality)	1
Oudhuis et al. [35] 2011	Netherlan	RCT	ICU patients (130	Probiotic group:	Probiotic group: 6g/d	discharge from	63.5±16.4/61.9±16.0	23±7.7/21±7.6	Clinical outcomes	5

	ds		/124)	received a solution of viable *Lactobacillus* plantarum 299/299v in a dose of $5*10^9$ colony forming units (cfu) (Probi AB, Lund, Sweden) two times daily Control: standard treatment		ICU,			(the duration of mechanical ventilation, hospital stay and mortality)	

Kaweesak et al.[22] 2010	Thailand	RCT	ICU patients with sepsis (17/17)	DF: received a mixed fiber formula contained 15.1 g / L of dietary fiber. [NutrenFibre®, Nestlé Suisse S.A. (Switzerland)] Control: received a standard formula without combined fiber [Nutren	DF:15.1 g / L	14d	49.2±20.5/51.9±17.4	39.9±8.5 40.1±8.6	Clinical outcomes (the duration of hospital stay and mortality)	4

				Optimum®, Nestlé Suisse S.A. (Switzerland)]						
Alenka et al.[23] 2007	UK	RCT	Surgical ICU patients (29/26)	DF: soluble fiber diet (Nova Source:2.2g fiber/100ml) Control: peptide diet (Nutricomp peptide) The target value of betw een	DF:20.5g (72 hours after admission)	7d	41(26-54)/ 41(26-54)	14(11-18)/13.5(10-18)	Intestinal permeability; clinical outcomes (the duration of mechanical ventilation)	3

				0.2 and 0.3 g/kg body weight / d and an average of 25 nonprotein kcal/ kg body weight / d at 72 hours after admission						
Karakan et al.[29] 2007	Turkey	RCT	ICU patients with AP (15/15)	DF: standard solution + multifiber supplement (24 g/ d) Control: standard soluti	DF:24g/d	discharge from ICU,	47.3±16.8/44.9±11.2	9.4±3.7/9.6±3.8	CRP; clinical outcomes (the duration of hospital stay and mortality)	4

				on						
Kotzampassi et al.[32] 2006	Greece	RCT	ICU patients with severe multiple trauma (35/30)	Probiotic+fiber group: the symbiotic preparation (Synbiotic 2000 Forte, Medipharm, Sweden) consisted of a combination of 10^{11} CFU of each of four probiotics as well as 2.5 g each of inulin, oat	DF:12g/d	15d	52.9±19/55.9±18	19.36±2.7/19.36±2.1	Systemic Inflammatory Response; clinical outcomes (the duration of mechanical ventilation and mortality)	4

				bran, pectin, and resistant starch. It was given in doses of 12 g per day diluted in 100 ml of tap water Control: powdered glucose polymer (maltodextrin, Caloreen, Nestle, UK)						
Kieft et al.[30] 2005	Netherlan	RCT	ICU patients (302/	DF: study formula	DF:4.5g-18g/d	discharge from	66.0 (49–74)/68.0 (55–74)	15.5 (12.0–20.3)/	Clinical outcomes	5

	ds		295)	(IMN：9 g Fiber /L) Control: isocaloric enteral formula.		ICU		17.0 (12.0 – 22.0)	(the duration of mechanical ventilation, hospital stay and mortality)	
Klarin et al.[31] 2005	Sweden	RCT	ICU patients (17/16)	Probiotic group: enteral formula + the test solution(consisted of a fermented oatmeal formula containing 10^9 colony-forming units	DF:3.35g/d	1w-3w	70.9(38–85)/57.5(34–76)	17 (13–29) / 19 (14–36)	Clinical outcomes (mortality)	3

				/ ml Lp 299v), every 6h Control: enteral formula						
De et al.[25] 2004	Brazil	RCT	Brain injury ICU patients (10/10)	DF：standard diet +30 g of glutamine and 240 ml of fermented milk with the probiotic strain Lactobacillus johnsonii (LC1®; Nestl´e, Sao	DF:30g DF+240 ml of fermented milk with the probiotic	5-14d	27 (19–46)/26 (19–49)	/	Clinical outcomes (the duration of mechanical ventilation and mortality)	3

				Paulo, Brazil) Control: standard diet. Caloric target was 35 kca / kg / day and 1.5 g of protein / kg / day						
Jain et al.[28] 2004	UK	RCT	ICU patients (45/45)	Symbiotic group: Trevis™ administered twice a day Control: sucrose and place	DF:15g/d	10d	72(62–77)/73(65–80)	11(9–14)/11(10–15)	Intestinal permeability; clinical outcomes (the duration of hospital stay and morta	5

				bo-capsules					lity)	
Mcnaught et al.[34] 2004	UK	RCT	ICU patients（52/51）	Probiotic group：conventional therapy + ProViva (containing $5*10^7$ colony forming units per ml of L.plantarum 299v).a target volume of 500 ml/d Control: conventional thera	DF：500 ml/d test solution	discharge from ICU,	71 (28-90)/71(28-87)	12(9–16)/12(8–17)	intestinal permeability; Systemic Inflammatory Response; mortality	3

				py						
Caparros et al.[24] 2001	Spain	RCT	ICU patients (122/98)	DF: Stresson Multifibre: 8.9 g/L. Caloric requirements were calculated as 25 kcal/kg per day Control: Nutrison Protein Plus; Nutricia Spain S.A., Madrid, Spain	DF：9-13.5g/d	7d	51(34-69)/58(37-69)	17(13-20)/16(13-21)	Clinical outcomes (mortality)	5
Spapen et al.[38] 2001	Belgium	RCT	ICU patients	DF: enteral	DF：22g/d	21d	68±11/69±15	26±7/24±8	clinical outco	5

			(13/12)	formula supplemented with 22 g of partially hydrolyzed guar per liter (Bene®ber, Novartis Nutrition, the Netherlands) Control: feed without fibers.					mes (mortality)	
schultz et al.[37] 2000	American	RCT	ICU patients (11/11)	DF: fiber-free formula + pectin	DF:1.07g/d	8d	66.5±19.2/72.8±13.1	17.9±6.33/17.8±4.0	Clinical outcomes (the duration of hospi	4

				Control: fiber-free formula					tal stay)	

DF = Fiber Group; Control = Control group; RCT: randomized controlled trial; ICU:intensive care units ; SCFA:short-chain fatty acids ; yr. :Year NOS: Newcastle-Ottawa scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; AP ： Acute pancreatitis.

Table 2. Results of Subgroup Analysis of the duration of mechanical ventilation by outcomes

Group	Reference No.	No. of study	MD (95%*CI*)	*P* value	I^2,% (*P*)
Total	23, 25, 26, 30, 32, 35	6	0.41(-1.89,2.72)	0.73	83(<0.01)
Type of supplement					
Fiber	23, 26, 30,	3	1.44(-0.30,3.17)	0.11	81(<0.01)
Probiotic	25, 35	2	2.19(-2.77, 7.14)	0.39	0(0.88)
Fiber+ Probiotic	32	1	-13(-19.69,-6.31)	<0.001*	-
Fiber supplementary dose (g/d)					
<20	25, 30, 32, 35	4	-3.07(-9.38,3.25)	0.34	81(<0.01)
≥20	26, 23	2	2.10 (0.90,3.30)	<0.001*	13(0.96)
Intervention time (d)					
≤ 7	26, 23	2	2.10 (0.90,3.30)	<0.001*	13(0.96)
>7	25, 30, 32, 35	4	-3.07(-9.38,3.25)	0.34	81(<0.01)
Type of ICU					
Surgical ICU	23,25, 32	3	-4.77 (-18.91,9.37)	0.51	90(<0.01)
General ICU	26, 30, 35	3	1.14(-0.51,2.80)	0.18	77(0.01)

*P<0.05

Group	Reference No.	No. of study	MD (95%*CI*)	*P* value	I^2,% (*P*)
Total	8, 22, 24, 26, 28, 29, 30, 35, 37	9	-3.16(-5.82, -0.49)	0.02*	53(0.03)
Type of supplement					
Fiber	22, 24, 26, 29,30, 37,	6	-3.61(-7.66, 0.45)	0.08	69(＜0.01)
Probiotic	8,28, 35	3	-3.12(-6.18, -0.07)	0.04*	0(0.58)
Fiber supplementary dose (g/d)					
＜20	24, 28, 30, 35, 37	5	-0.41(-3.03,2.21)	0.76	15(0.32)
≥20	22, 26, 29,8	4	-5.62(-8.04,-3.21)	＜0.001*	0(0.43)
Intervention time (d)					
≤7	26, 29, 23, 24	3	-3.90(-10.19,2.40)	0.22	79(＜0.01)
＞7	22, 28, 30, 23, 35, 37,8	6	-2.12(-4.47,0.24)	0.08	13(0.33)
Type of ICU					
Medical ICU	29,8	2	-4.77(-7.48,-2.07)	＜0.001*	0(0.86)
Surgical ICU	22	1	-5.20 (-20.26,9.86)	0.50	-
General ICU	24, 26, 28, 30, 35, 37	6	-2.47(-6.34,1.39)	0.21	63(0.02)

Table 3. Results of Subgroup Analysis of the duration of hospital stay by outcomes

*P＜0.05

Table 4. Results of Subgroup Analyses of mortality by outcomes

Group	Reference No.	No. of study	OR (95%*CI*)	*P* value	I^2,% (*P*)
Total	22, 24, 25, 28,29, 30,31, 32,34, 35, 36, 38	12	0.87(0.68,1.11)	0.28	8(0.37)
Type of supplement					
Fiber	2,24, 29, 31, 34, 38	6	0.89(0.66, 1.21)	0.46	8(0.37)
Probiotics	25, 28, 34, 35, 36	5	0.91(0.59,1.40)	0.67	35(0.20)
Fiber+ Probiotics	32	1	0.39(0.11,1.33)	0.13	-
Fiber supplementary dose (g/d)					
<20	24, 25, 28, 30, 31, 32, 34, 35	8	0.95(0.74,1.23)	0.72	0(0.71)
⩾20	22, 29, 36, 38	4	0.18(0.06,0.57)	0.004*	0(0.83)
Intervention time (d)					
⩽7	24,28, 29	3	0.78(0.47,1.30)	0.34	21(0.28)
>7	22, 25, 30,31, 32, 34, 35, 36, 38	9	0.89(0.68,1.18)	0.43	23(0.25)
Type of ICU					
Medical ICU	29, 36	2	0.13(0.03, 0.65)	0.01*	0(0.66)
Surgical ICU	22, 25, 32	3	0.40 (0.13,1.22)	0.11	0(0.90)
General ICU	24, 28, 30, 31, 34, 35, 38	7	0.97(0.75,1.25)	0.81	0(0.71)

*P<0.05