Journal of Critical Care 53 (2019) 142–148

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Diarrhea and patient outcomes in the intensive care unit: Systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Diarrhea
Intensive care unit
Mortality
Length of stay
Systematic review
Meta-analysis

ABSTRACT

Purpose: We aimed to determine whether diarrhea experienced by patients in the intensive care unit (ICU) is related to their clinical outcomes.
Material and methods: We performed a systematic review and meta-analysis. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, and the World Health Organization International Clinical Trials Registry Platform between inception and August 2018. The primary outcome was ICU mortality, and secondary outcomes included hospital mortality, ICU length of stay, hospital length of stay. The quality of evidence was determined using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.
Results: Twelve studies (enrolling 13,140 patients) compared patients with diarrhea to patients without diarrhea in the ICU. Diarrhea was related to ICU mortality (relative risk [RR]: 1.43; 95% confidence interval [CI]: 1.03 to 1.98). The mean difference (MD) in ICU length of stay between patients with and without diarrhea was 8.08 days (95% CI: 5.85 to 10.32), while the MD in hospital length of stay was 9.67 (95% CI: 2.17 to 17.16). The certainty of evidence for these outcomes was low.
Conclusions: The diarrhea experienced by patients may be associated with higher mortality and prolonged length of stay in the ICU and hospital.

1. Introduction

Diarrhea is a common problem for patients in the intensive care unit (ICU) [1] that causes substantial discomfort, and dealing with diarrhea increases both the workload of ICU caregivers and the cost of care [2]. Many factors may cause diarrhea, including enteral nutrition and drugs (e.g. laxatives and antibiotics) [1]. The introduction of a bowel management protocol can assist in preventing diarrhea in the ICU population [3].

Recent studies have reported that patients with diarrhea had a longer ICU length of stay than those without [4,5]. On the other hand, studies evaluating the relationship between diarrhea and mortality have yielded inconsistent results [4-6]. At present, no systematic reviews or meta-analyses have reported the relationship between diarrhea and clinically relevant outcomes in patients admitted to ICU. Therefore, in the present study, we aimed to evaluate the available literature and determine whether diarrhea experienced by patients in the ICU is related

Abbreviations: ICU, intensive care unit; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; CENTRAL, Cochrane Central Register of Controlled Trials; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform; QUIPS, Quality in Prognostic Studies; RR, risk ratio; CI, confidence interval; MD, mean difference; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; APACHE, Acute Physiology And Chronic Health Evaluation.

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https://doi.org/10.1016/j.jcrc.2019.06.014
0883-9441/

to clinically relevant outcomes such as mortality, ICU length of stay, and hospital length of stay.

2. Materials and methods

2.1. Compliance with reporting guidelines

Using a pre-specified protocol (PROSPERO registry ID: CRD42018105511) [7], we conducted a systematic review of the relevant literature in agreement with the recommendations listed in the Cochrane Handbook [8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [9]. We confirmed that this systematic review is PRISMA-compliant by consulting the PRISMA 2009 checklist [10] (see Appendix A) and meta-analysis of observational studies in epidemiology (MOOSE) [11].

2.2. Research question and eligibility criteria

The review question was: "Is diarrhea experienced by patients admitted to the ICU related to their short-term clinical outcomes (in the ICU and hospital) and long term outcomes (after discharge from hospital)?" We included published and unpublished trials and observational studies with control groups (adult human subjects age ≥ 18 years), of any race and gender, admitted to the ICU, including abstracts and letters. Studies in any language and from any country were accepted, and we included studies with any length of follow-up. We excluded case reports and case series. The exposure was patients with diarrhea in the ICU, as defined by the authors, including references to stool consistency, stool frequency, and/or stool volume (weight). The control group consisted of patients without diarrhea.

2.3. Outcomes of interest

The primary outcome was ICU mortality and secondary outcomes included hospital mortality, ICU length of stay, hospital length of stay, cost, and any outcomes after hospital discharge.

2.4. Search strategy and selection of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, EMBASE via ProQuest, CINAHL via EBSCOhost, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search portal. The search was performed in August 2018 using a set of suitable search terms (see Appendix B). We manually searched reference lists for guidelines on gastrointestinal function in ICU patients [12]. We also attempted to identify other relevant research by manually searching the reference lists of studies returned by the search and those of articles citing such studies (based on citation information from the Web of Science). If a candidate study did not contain the necessary information, we contacted the study authors. Three reviewers (Shunsuke Taito, Yusuke Kawai, and Takashi Ariie) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The three reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the three reviewers, occasionally with arbitration by a fourth reviewer (Yuki Kataoka).

2.5. Data abstraction and quality assessment

Two reviewers (Shusnuke Taito and Yusuke Kawai) independently extracted study-level data using pre-specified forms. We used the crude number to pool from each study. Disagreements regarding data extraction were resolved through discussions. Where necessary, we contacted the authors of studies that did not provide sufficient information. The risk of bias in each study was assessed independently by two reviewers (Shunsuke Taito and Yusuke Kawai) using the Quality in Prognostic Studies (QUIPS) tool [13]. We assessed the domain of study confounding using the QUIPS tool; however, we did not consider the domain for judging evidence certainty since the aim of our study aim was to explore the relationship and not causality. Differences in opinions regarding the assessment of the risk of bias were resolved through discussion between the two reviewers, occasionally with arbitration by a third reviewer (Yuki Kataoka).

2.6. Data analysis

All analyses were conducted using Stata software, version 15.0 (Stata Corp., College Station, TX, USA). For the dichotomous variables of mortality, pooled risk ratios (RRs) with 95% confidence intervals (CIs) were provided. For continuous outcomes including length of stay, the standardized mean differences, or the mean differences (MD) with 95% CIs were calculated. We used random-effects models for all analyses. We calculated I^2 as a measure of variation across studies due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%, negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity was identified for an outcome ($I^2 > 50\%$), we investigated the underlying reasons and conducted an χ^2 test, with a P-value of <0.10 indicating statistical significance. We investigated publication bias by checking the WHO ICTRP to detect trials that had been completed but not published at the time of the review.

We planned the following pre-specified sensitivity analyses for the primary outcomes: (i) exclusion of studies using imputed statistics, (ii) exclusion of studies using the definition of diarrhea without stool weight or volume, and (iii) when the meta-analytic result of the primary outcome was statistically significant, we adjusted the following confounders using meta-regression: age, proportion of women, illness severity or organ failure score, and ICU length of stay. We also carried out pre-specified subgroup analyses according to the definition of diarrhea (definition with stool volume [weight] or without stool volume [weight]), and the timing of the commencement of diarrhea (before ICU admission or after ICU admission). Statistical significance was set at $P < .05$. We created a summary-of-findings table that included an overall grading of evidence certainty for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [14,15].

3. Results

3.1. Characteristics of included studies

Among the 3167 studies retrieved following database and manual searches, we identified 12 unique studies [4-6,16-24] that fulfilled all eligibility criteria and were included in the qualitative synthesis (Fig. 1, Table 1). The 12 studies provided a pooled sample of 13,140 patients admitted to the ICU. The mean or median age in the analyzed studies ranged from 25 to 67.2 years, while the mean or median Acute Physiology And Chronic Health Evaluation (APACHE) II score ranged from 12.1 to 30. Many studies had definitions of diarrhea including reference to stool consistency and frequency without stool volume (weight) [4-6,16,18,19,22-24]. Only one study had a definition of diarrhea including stool weight by the King's Stool Chart [21]. In patients in five studies, the commencement of diarrhea occurred after ICU admission [4,18,19,22,24]; the timing was unknown for the other studies. Two studies [16,20] did not have sufficient outcome data for a meta-analysis (see Appendix C), leaving a total pooled sample of 12,624 patients (1888 patients in the exposure group; 10,736 controls) represented across 10 studies to be included in the quantitative synthesis. We did not identify any ongoing studies.

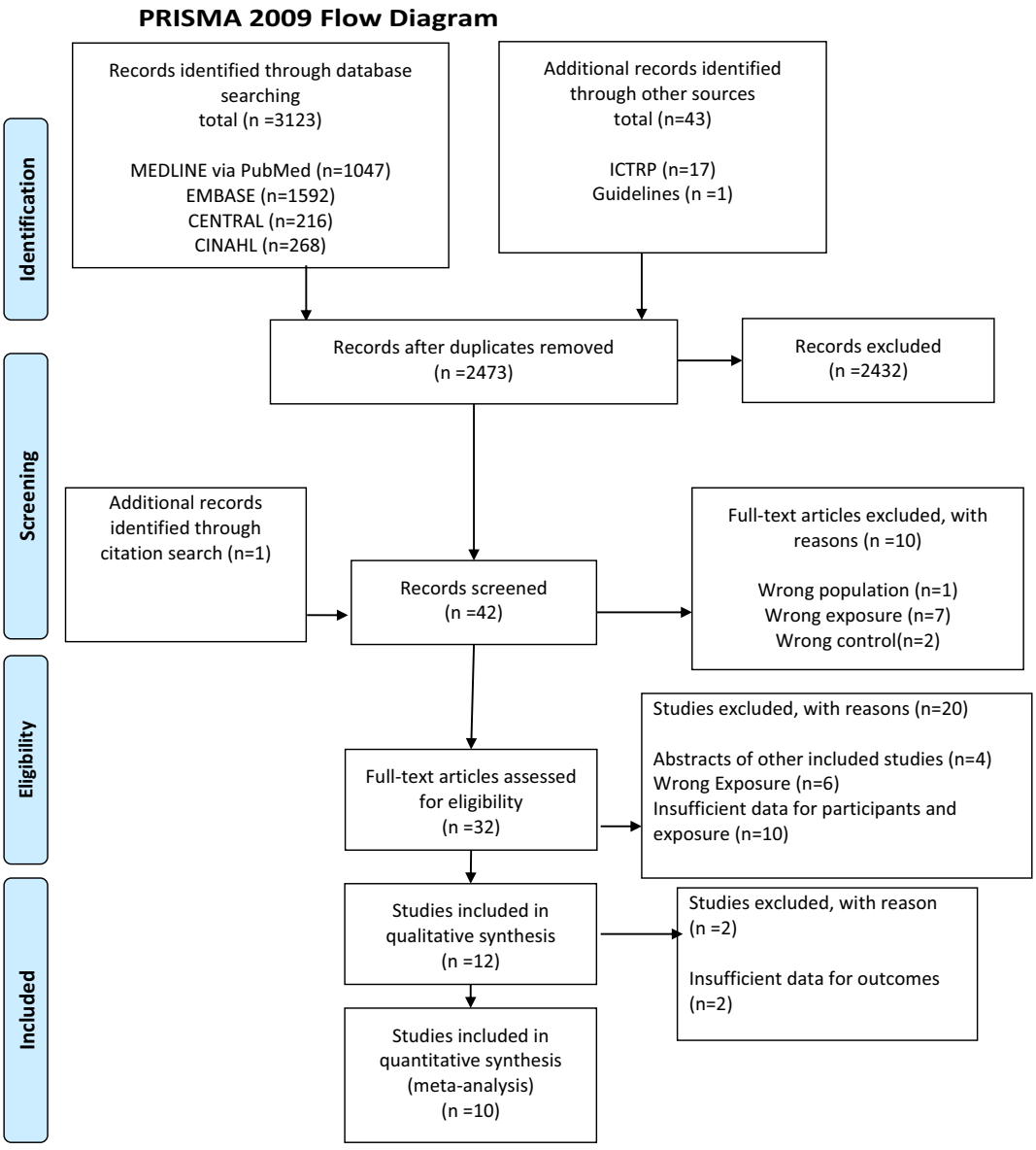

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram.

Most studies were at a moderate risk of bias (Table 2). Almost all studies demonstrated low risk of bias for study participation, study attrition, and outcome measurement. However, three studies had a high risk of bias for prognostic factor measurement and six studies had a moderate risk of bias for prognostic factor measurement. All studies demonstrated moderate or high risk of bias for study confounding because all important confounding factors, such as antibiotic use and inflammatory bowel disease, were not considered. Also, 10 studies had a moderate risk of bias for statistical analysis and reporting because they were not registered, except for a randomized controlled trial.

3.2. Primary and additional outcomes

ICU mortality was reported in eight studies (Fig. 2a). Diarrhea was significantly related to ICU mortality (RR: 1.43; 95% CI: 1.03 to 1.98; $I^2 = 86.7\%$; $n = 11{,}866$). The certainty of evidence for ICU mortality was low (Table 3). We could not carry out all pre-specified sensitivity analyses because none of the studies used imputed statistics; only one study used a definition of diarrhea that included stool weight or volume, and the primary outcome was not statistically significant. The pre-specified subgroup analysis for the primary outcome revealed a very similar result in each sub-group (see Appendix D). In our protocol, we defined the participants as adults, aged 18 years and older, of any race and gender, admitted to the ICU. Two of the studies used in our quantitative synthesis [17,18] included a few patients who were under 18 years old. We performed additional sensitivity analysis excluding one study [18] which reported ICU mortality, and found that diarrhea was not significantly related to ICU mortality (RR: 1.39; 95% CI 0.92 to 2.12; $I^2 = 87.9\%$; $n = 11{,}409$) (see Appendix E).

ICU length of stay was measured in nine studies (Fig. 2b). The MD in ICU length of stay between patients with and without diarrhea was 8.08 days (95% CI 5.85 to 10.32). The MD in hospital length of stay was 9.67 (95% CI 2.17 to 17.16) in two studies (Fig. 2c). The certainty of evidence for ICU length of stay and hospital length of stay were low (Table 3). No studies reported other outcomes such as cost or any outcomes after hospital discharge.

4. Discussion

The results of the present review covering 12 studies and 13,140 patients suggest that diarrhea in the ICU was significantly related to ICU mortality, ICU, and hospital length of stay among patients admitted to

Table 1
Characteristics of the studies analyzed in this review.

Author, year, country	No. of participants	Study type	Exposure	Outcomes	Notes
Guenter et al., 1991, United States	100 (Diarrhea 30, No diarrhea 70)	Single-center prospective cohort study	Diarrhea was defined as three or more loose or watery stools per day. Timing of the commencement of diarrhea was unclear.	ICU length of stay	Participants required tube feeding for at least 5 days.
Wu et al., 2004, China	735 (Diarrhea 86, No diarrhea 649)	Single-center retrospective cohort study	Definition of diarrhea and timing of the commencement of diarrhea were unclear	ICU length of stay	Participant age ranged from was 6–91 years old.
Borges et al., 2008, Brazil	457 (Diarrhea 135, No diarrhea 322)	Single-center prospective cohort study	Diarrhea was defined as two loose or watery stools per day for at least two consecutive days. Timing of the commencement of diarrhea was 5.3 ± 3.9 days after ICU admission.	ICU mortality, ICU length of stay, hospital length of stay	Participants included 6 patients (1.3%) who were <18 years old.
Reintam et al., 2009, Estonia	1312 (Diarrhea 184, No diarrhea 1128)	Single-center prospective cohort study	Diarrhea was documented when non-formed stools occurred at least three times per day. Timing of the commencement of diarrhea was unclear.	ICU mortality	
Thibault et al., 2013, Switzerland	278 (Diarrhea 38, No diarrhea 240)	Single-center prospective cohort study	Diarrhea was defined as the elimination of at least three liquid stools per day after ICU admission.	ICU mortality, ICU length of stay	
Ozgur et al., 2016, Turkey	158 (Diarrhea 78, No diarrhea 80)	Single-center retrospective cohort study	Diarrhea was defined as loose or watery stools and three or more episodes of liquid stools a day after ICU admission.	ICU mortality, ICU length of stay, hospital length of stay	A control group was formed of patients without diarrhea but with comparable demographic features.
Dionne et al., 2016, Canada	338 (More than one third patients had diarrhea)	Multi-center prospective cohort study	Definition of diarrhea was classified three ways: 1) as three or more liquid bowel movements per day defined as Bristol type 7 (WHO Criteria), 2) any Bristol type 6 or 7 stool, and 3) a Bliss score of 4. The timing of the commencement of diarrhea was unclear.	ICU mortality, hospital mortality, ICU length of stay, hospital length of stay	Published as an abstract. The rates of diarrhea were different between definitions.
Tirlapur et al., 2016, United Kingdom	9331 (Diarrhea 1207, No diarrhea 8124)	Single-center retrospective cohort study	Diarrhea was defined as loose stools, according to the Bristol Stool Chart. The timing of the commencement of diarrhea was unclear.	ICU mortality, ICU length of stay	
Jakob et al., 2017, Switzerland	90 (Diarrhea 60, No diarrhea 30)	*Re*-analysis of a single-center pilot RCT	Diarrhea was defined as a score of 15 or more during one day using the King's Stool Chart. The timing of the commencement of diarrhea was unclear.	ICU mortality, ICU length of stay, hospital length of stay	This study assessed diarrhea and the respective effects of a modified enteral diet compared to a standard diet for patients with ICU stay ≥5 days and tube feeding ≥3 days.
Vieira et al., 2018, Brazil	23 (Diarrhea 16, No diarrhea 7)	Single-center prospective cohort study	Diarrhea was defined as three or more episodes of liquid or semi-liquid stools 24 h after ICU admission.	ICU length of stay	Participants were patients with a traumatic brain injury using nutritional therapy.
de Barros et al., 2018, Brazil	103 (Diarrhea 48, No diarrhea 55)	Single-center prospective cohort study	Diarrhea was defined as the presence of three or more liquid or pasty stools in 24 h. Timing of the commencement of diarrhea as unclear.	ICU mortality, ICU length of stay	Participants used exclusive enteral nutritional therapy.
Atasever et al., 2018, Turkey	137 (Diarrhea 36, No diarrhea 101)	Single-center prospective cohort study	Diarrhea was defined as the elimination of at least three liquid stools per day after ICU admission.	ICU mortality, ICU length of stay	Participants received nasogastric tube feeding in the ICU.

ICU, intensive care unit; RCT, randomized controlled trial.

the ICU. Furthermore, despite the large sample size in the meta-analysis for ICU mortality and ICU length of stay, the certainty of evidence was low.

Diarrhea experienced by patients in the ICU may be associated with higher mortality. Diarrhea can cause water and electrolyte imbalance, metabolic acidosis, and malnutrition [1]. Although the possibility of immortal time bias cannot be ignored (some patients may die before diarrhea occurrence), diarrhea itself may be related to mortality in patients admitted to the ICU. Diarrhea could be considered as a sign of organ failure that is associated with a higher risk of mortality. On the other hand, almost all studies that reported an illness severity score related to mortality [4,5,17,18,21,24] reported that patients with diarrhea had a significantly higher illness severity score at ICU admission than that of patients without diarrhea. Enteral delivery of >60% of energy targets [4] and exposure to antimicrobial drugs [25] and laxatives [3] increases the risk of diarrhea; these interventions are part of the treatment regime for more severely ill patients in the ICU. Diarrhea might just be a symptom in more severe patients.

Similarly to increased mortality, diarrhea in the ICU may be associated with prolonged length of stay in both the ICU and hospital, whereas causality remains unclear. The factors associated with diarrhea (malnutrition, electrolyte abnormalities, dehydration) may impair recovery from initial critical illness. On the other hand, reverse causality cannot be ruled out. Triggers of diarrhea, such as infection, medication, and enteral/tube feeding [1], may be associated with a severe condition, which may lead to an increase in the ICU length of stay and hospital length of

Table 2
Assessment of the risk of bias in analyzed trials.

Author, Year (Ref.)	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Guenter et al., 1991 (15)	Low	Low	Moderate	Low	High	Moderate
Wu et al., 2004 (16)	Low	Low	High	Low	Moderate	Moderate
Borges et al., 2008 (17)	Low	Low	Low	Low	Moderate	Moderate
Reintam et al., 2009 (6)	Low	Moderate	Moderate	Low	High	Moderate
Thibault et al., 2013 (4)	Low	Low	Moderate	Low	Moderate	Moderate
Ozgur et al., 2016 (18)	Low	Low	High	Low	Moderate	Moderate
Dionne et al., 2016 (19)	Low	Low	Moderate	Low	High	High
Tirlapur et al., 2016 (5)	Low	Low	High	Low	Moderate	Moderate
Jakob et al., 2017 (20)	Low	Low	Low	Low	Moderate	Low
Vieira et al., 2018 (21)	Low	Low	Low	Low	Moderate	Moderate
de Barros et al., 2018 (22)	Low	Low	Moderate	Low	High	Moderate
Atasever et al., 2018 (23)	Low	Low	Moderate	Low	High	Moderate

stay. Future studies that evaluate the association between early onset diarrhea and ICU length of stay are needed to clarify this question.

Cost and outcomes after hospital discharge, such as skin problems, quality of life, and long-term mortality, were not reported in any included studies, and we could not evaluate the association between diarrhea and cost or outcomes after hospital discharge in patients admitted to the ICU. Diarrhea was associated with prolonged ICU length of stay in this review; therefore, it is plausible that diarrhea would be associated with increased medical resources and costs. Intensive care survivors have frequently reported a wide range of impairments in their health status which may last for months or years after hospital discharge [26]. For example, patients with delirium were at an increased risk of cognitive impairment after hospital discharge, in addition to increased mortality and hospital length of stay [27]. Further studies are needed to determine the relationship between diarrhea and outcomes after hospital discharge.

The present review has several strengths. The results of this review were based on the best available evidence following a comprehensive search. In addition, we employed rigorous methodology that followed a written, a priori protocol developed according to the PRISMA statement [9] and MOOSE proposal [11], duplicate assessment of eligibility,

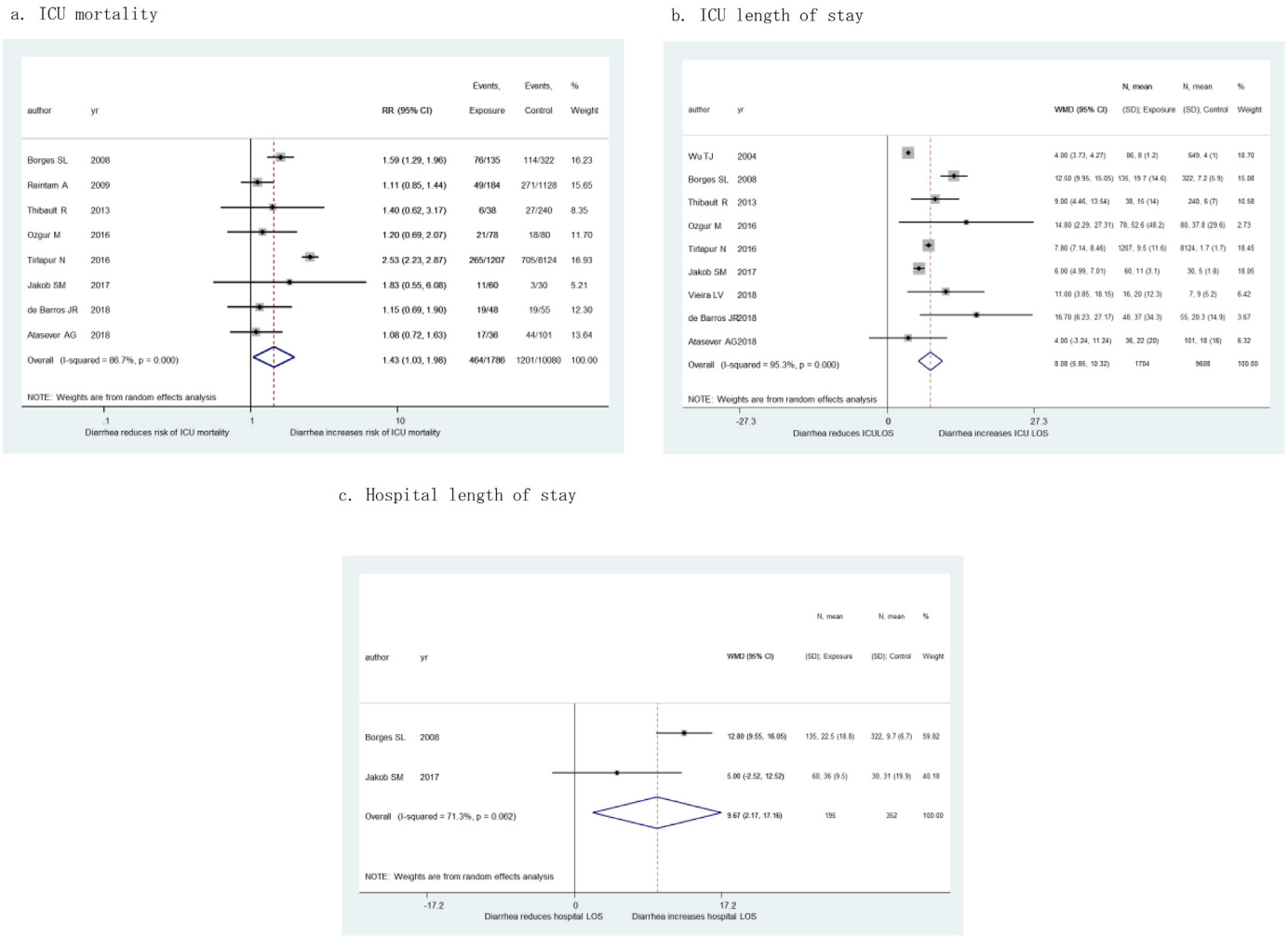

Fig. 2. Forest plot for ICU mortality, ICU length of stay, and hospital mortality.

Table 3
Findings from 12 trials focused on diarrhea in the ICU.

Overview of study design						
Patients or study population: adult patients admitted to ICU						
Exposure: Diarrhea, defined including reference to stool consistency, stool frequency, and/or stool volume (weight)						
Comparison: No diarrhea						
Outcome	Illustrative comparative risks*(95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Intervention				
ICU mortality	Study population		RR 1.43	11,866	⊕⊖⊖	
	350 per 1000	501 per 1000 (361 to 693)	(1.03 to 1.98)	(8 studies)	Low[a,b,c]	
ICU length of stay	Study population			11,312	⊕⊕⊖⊖	
		MD: 8.08 (5.85 to 10.32)		(9 studies)	Low[a,b,c]	
Hospital length of stay	Study population			547	⊕ ⊕ ⊖⊖	
		MD: 9.67 (2.17 to 17.16)		(2 studies)	Low[a,c,d]	
*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group. Assumed risk was estimated from the meta-analysis of control risks.						
GRADE Working Group grades of evidence						
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.						
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.						
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.						
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of						

ICU, intensive care unit; CI, confidence interval; RR, risk ratio; MD, mean difference; RCT, randomized controlled trial.
[a] We did not consider the domain of study confounding in the risk of bias for judging the certainty of the evidence.
[b] Downgraded one point because of moderate or high risk of bias associated with prognostic factor measurement, statistical analysis, and reporting.
[c] Downgraded one point for inconsistency.
[d] Downgraded one point as it was imprecise (only two studies).

risk of bias, and data abstraction, and used the GRADE approach [14,15] for assessing the certainty of evidence.

This systematic review has four potential limitations. First, our study aim was to explore relationships with ICU mortality, but not to define causality. In other words, we perceived diarrhea as a marker, not a player. No studies reported the adjusted results appropriately. We could not consider the causes of diarrhea, including enteral nutrition and drugs, as many included studies did not describe these episodes in sufficient detail. To explore a potential causal relationship, futures studies that take into consideration confounding factors and the cause of diarrhea are needed. Second, the lack of a cohesive definition of diarrhea used within the studies may have affected the results. For example, diarrhea was defined as three or more loose or watery stools per day, two loose or watery stools per day for at least two consecutive days, or a score of 15 or more in one day using the King's Stool Chart. For the ICU population, diarrhea is defined by the Working Group on Abdominal Problems of the European Society of Intensive Care Medicine (ESICM) as having three or more loose or liquid stools per day with a stool weight >200–250 g/day [12]. Further studies that include stool volumes in the definition, such as that found in the ESICM definition [12], are necessary to clarify the relationship between diarrhea and patient outcomes. Third, the statistical heterogeneity of ICU mortality and ICU hospital length of stay were high. We could not perform meta-regression to explore the effect of the high heterogeneity because studies that included subgroup analysis were limited. Fourth, there may be immortal time bias (some patients may have died before diarrhea occurrence). To help reduce the immortal time bias, we could not perform an analysis strictly related to early onset diarrhea in the ICU and the effect of ICU length of stay because limited information was provided regarding the onset of diarrhea in the included studies.

5. Conclusions

Diarrhea experienced by patients may be associated with higher mortality and prolonged length of stay, whereas causality remains unclear. Further well-designed studies focusing on the cause of diarrhea and the timing of the commencement of diarrhea are needed to confirm our findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.014.

Acknowledgments

We thank Dr. Daren K. Heyland (Department of Critical Care Medicine, Queen's University), Prof. Deborah J. Cook (Departments of Medicine, Health Research Methods, Evidence, and Impact, McMaster University), Dr. Evren Senturk (Anesthesiology and Intensive Care, Koc University Hospital), Dr. litao Guo (Department of Critical Care Medicine, First Affiliated Hospital of Xi'an Jiaotong University), Dr. Joanna Dionne (Postgraduate Medical Education, McMaster University), Dr. Josiane Rodrigues de Barros (Hospital Universitário da Universidade Federal de Sergipe), Dr. Julio Maria Fonseca Chebli (Disciplina de Anatomia do Instituto de Ciências Biológicas, Universidade Federal de Juiz de Fora), Dr. Nermin Kelebek Girgin (Department of Anesthesiology and ICU, Uludag University Hospital), Ms. Peggi Guenter (Senior Director of Clinical Practice, Quality, and Advocacy American Society for Parenteral and Enteral Nutrition (ASPEN)), Dr. Reintam Blaser A (Department of Anaesthesiology and Intensive Care, University of Tartu), Dr. Stephan M. Jakob (Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern) for providing us with additional information regarding their studies. We would like to thank Editage (http://www.editage.jp) for English language editing.

Authors' contributions

Shunsuke Taito, Yasushi Tsujimoto, Masahiro Banno, and Yuki Kataoka designed the study. Shunsuke Taito, Yusuke Kawai, Takashi Ariie and Yuki Kataoka were involved in the systematic review process. Shunsuke Taito analyzed and interpreted the data, and drafted the manuscript. Yusuke Kawai, Keibun Liu, Takashi Ariie, Yasushi Tsujimoto, Masahiro Banno, and Yuki Kataoka critically reviewed the initial manuscript, and approved the final manuscript as submitted.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interests

None.

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