Association between diarrhea quantity and in-hospital mortality in intensive care unit patients: A retrospective cohort study

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Research

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Abstract

Background

Previous studies have shown that diarrhea is associated with increased mortality of patients in intensive care units (ICUs). However, these studies used dichotomized cutoff values, even if diarrhea was a continuous condition. This study aimed to assess the association between diarrhea quantity and mortality in ICU patients with newly developed diarrhea.

Methods

We conducted this single-center retrospective cohort study at the Kameda Medical Center ICU. We consecutively included all adult ICU patients with newly developed diarrhea in the ICU between January 2017 and December 2018. Newly developed diarrhea was defined based on a Bristol stool chart scale ≥ 6 and frequency of diarrhea ≥ 3 times per day. We excluded patients who already had diarrhea on the day of ICU admission among other criteria. We collected data on the quantity of diarrhea on the day when patients newly developed diarrhea. The primary outcome was in-hospital mortality. The risk ratio (RR) and 95% confidence interval (CI) for the association between the quantity of diarrhea and mortality were estimated using multivariable-modified Poisson regression models adjusted for the Charlson Comorbidity Index, sequential organ failure assessment score, and serum albumin levels.

Results

Among 231 participants, 68.4% (158/231) were men; the median age of the patients was 72 years. The median quantity of diarrhea was 401 g (interquartile range [IQR] 230–645 g), and in-hospital mortality was 22.9% (53/231). More diarrhea at baseline was associated with higher in-hospital mortality; the unadjusted RR (95% CI) per 200-g increase was 1.10 (1.01–1.19). This association remained in the multivariable-adjusted analysis; the adjusted RR (95% CI) per 200-g increase was 1.10 (1.01–1.20).

Conclusions

A greater quantity of diarrhea was an independent risk factor for in-hospital mortality. The quantity of diarrhea may be an indicator of disease severity in ICU patients.

Background

Diarrhea is a common gastrointestinal symptom in the intensive care unit (ICU), with an incidence of 10–78% [1]. In ICU patients, enteral nutrition (composition, osmolarity, speed, intermittent or continuous, fiber), drugs (e.g., antibiotics, laxatives), infectious diseases (e.g., *Clostridium difficile* infection [CDI]), and comorbidity (e.g., anemia, cirrhosis) are common causes of diarrhea [2]. The effects of diarrhea include

increased risk of contamination of devices and wounds, dehydration, electrolyte abnormalities, and malabsorption [3–5].

Several studies have shown an association between diarrhea and mortality [6–14], and this association remained even in ICU patients without CDI [8]. Taito et al. conducted a systematic review and demonstrated that diarrhea was associated with the length of hospital stay and ICU mortality [14]; however, all previous studies defined diarrhea based on dichotomized criteria with respect to consistency and frequency. The European Society of Intensive Care Medicine (ESICM) has adopted dichotomized criteria for the quantity of diarrhea as a component of the definition of diarrhea in the ICU [3]. However, healthcare providers need to make decisions based on continuous conditions rather than dichotomized conditions in practice [15, 16]. For example, more diarrhea may cause worse electrolyte imbalance, nutritional deficit, and hemodynamic instability owing to water loss [17, 18], which leads to changes in clinical management. Moreover, more diarrhea may result in more deaths. To clarify this, it is necessary to quantify the relationship between the quantity of diarrhea and death.

This retrospective cohort study aimed to investigate the association between the quantity of diarrhea and mortality in ICU patients with newly developed diarrhea.

Methods

Study design and setting

We conducted this single-center retrospective cohort study at Kameda Medical Center ICU. This study was reviewed and approved by the institutional review board of Kameda Medical Center and Kyoto University. These committees waived the requirement of informed consent from all participants enrolled in this study because of the retrospective study design. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

Study population

From January 2017 to December 2018, we consecutively included all patients aged ≥ 18 years with newly developed diarrhea in the ICU. We defined newly developed diarrhea in the ICU as three or more loose or liquid stools per day according to the World Health Organization (WHO) definition [20]. To include patients with newly developed diarrhea in the ICU, the following patients were excluded on the day of ICU admission: patients with a stoma, chronic diarrhea (e.g., inflammatory bowel syndrome, short bowel syndrome), post-gastrointestinal surgery, gastrointestinal bleeding, or bacterial and viral enteritis (including *Clostridium difficile* enteritis and cytomegalovirus enteritis) or those who already had diarrhea on the day of ICU admission. In addition, patients readmitted to the ICU and those who died on the day of admission were excluded.

Data collection

We collected data such as age, sex, admission category (medical or surgery), sepsis defined by sepsis-3 [21], ICU readmission, Charlson Comorbidity Index (CCI) [22], and treatment limitation (limitations in providing ICU-specific life-sustaining therapies such as mechanical ventilation, cardiopulmonary resuscitation) from electronic health record reviews. Other data such as Acute Physiology and Chronic Health Evaluation (APACHE) II score [23], Simplified Acute Physiology Score (SAPS) II [24], Sequential Organ Failure Assessment (SOFA) score [25], potential causes of diarrhea (proton pump inhibitor, enteral nutrition, antibiotics, laxative drugs), testing for CDI (glutamate dehydrogenase test, CD toxin, or stool culture), and biopsy-diagnosed cytomegalovirus enteritis were also collected. We refer to CCI with age score as “CCI” and defined CCI without age score as “CCI without age score.”

Measurement of diarrhea

Stool data of ICU patients were collected from electronic health records. Nurses routinely checked the presence or absence of stools every 2–4 h. If there was a stool, consistency and quantity were assessed. Each stool sample was evaluated using the Bristol Stool Chart Scale (BSCS) [26]. The BSCS is a 7-point scale in which stools are scored according to cohesion and surface cracking as follows: 1. separate hard lumps like nuts; 2. sausage shaped but lumpy; 3. like a sausage or snake but with cracks on its surface; 4. like a sausage or snake and smooth and soft; 5. soft blobs with a clear-cut edge; 6. fluffy pieces with ragged edges and mushy; and 7. watery with no solid pieces. A BSCS of 6 or 7 is classified as diarrhea [27, 28]. This scale has been evaluated for its concordance and is a widely used scale [28–34]. The quantity of stool was measured using a weight scale and recorded in the electronic medical records. Since most ICU patients had urinary catheters, contamination of the stool by urine was minimized. The main exposure was the quantity of diarrhea per day on the day of the diarrhea diagnosis. The daily quantity of diarrhea was calculated from calendar days (total quantity from 0:00 to 24:00). These data were collected from the electronic health records.

Outcome measurement

The primary outcome was in-hospital mortality. Secondary outcomes included ICU, 28-day, and 90-day mortalities; ICU-free days at the 28th day [35]; and hospital-free days at the 90th day [36]. In these free days, we used the event-free survival day (the number of event-free days was considered to be zero for patients who died in the time frame) to measure these outcomes [33, 34, 38].

Statistical analyses

Patient characteristics are described as median and interquartile range (IQR). Modified Poisson regression models were used to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for the association between the quantity of diarrhea (per 200-g increase) and in-hospital mortality [37, 38]. The reason for using the unit of 200 g is that the ESICM definition of diarrhea is 200–250 g [3]. The multivariable analysis was adjusted for CCI, SOFA score, and serum albumin levels. These covariates were selected a priori based on clinical plausibility and previous studies [2, 8, 13]. We performed multiple imputations for missing values using multiple imputations by chained equation (MICE) with 50 iterations that generated 100 datasets with imputed missing values [39, 40].

To perform sensitivity analyses, we tested several modified Poisson regression models to assess the robustness of the primary analysis. First, we adjusted for the following covariates: model 1 for age, sex, CCI without age score, SOFA score, and serum albumin; model 2 for CCI, APACHE II score, and serum albumin; model 3 for CCI, SAPS II score, and serum albumin; and model 4 for CCI, SOFA score, serum albumin, and enteral nutrition. Second, we conducted a complete case analysis. Third, because CDI and cytomegalovirus enteritis affect mortality, we performed a further analysis excluding patients diagnosed with them after ICU admission. Finally, instead of using continuous data (the actual quantity of diarrhea), we used categorical data (near quartiles of the quantity of diarrhea) for the primary model.

We applied the same analyses as that for the primary outcome to assess the association between the quantity of diarrhea (per 200-g increase) and the following secondary outcomes: ICU mortality, 28-day mortality, and 90-day mortality.

We reported 95% CIs as an informal measure of uncertainty and avoided using terms such as statistical significance according to the recommendation of the American Statistical Association [41]. The analyses were performed using R software, version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria; <https://www.R-project.org/>).

Results

Patient characteristics

During the study period, 1579 adult patients were admitted to the ICU, and 334 patients with newly developed diarrhea were included in this study. Among those patients, 103 were excluded. Finally, 231 patients were included in the analysis (Fig. 1).

The median age of patients was 72 (IQR [64, 80]) years, 158/231 (68.4%) patients were men, median CCI was two (IQR [1, 3]), median APACHE II score was 21 (IQR [14, 28]), and median SOFA score was 9 (IQR [6, 12]). Patients admitted for nonoperative reasons were the most prevalent (162/231, 70.1%). Sepsis was diagnosed in 121 patients (52.4%). Antimicrobials and laxative drugs as possible causes of diarrhea were administered to 214/231 (92.6%) and 119/231 (51.5%) patients, respectively. Overall, 2/231 (0.9%) patients were diagnosed with CDI in the ICU, and two (0.9%) patients were diagnosed with CMV by colonoscopic biopsy in the ICU. The median number of days from ICU admission to newly developed diarrhea was 3 (IQR [2, 6]), and the median quantity of diarrhea was 401 (IQR [230.5, 645]) g. Other patient characteristics on ICU admission are summarized in Table 1. Three patients had missing values for the severity score because arterial blood gas was not measured. There were no missing measurements for other variables, including the quantity of diarrhea.

Table 1
Baseline characteristics of the study patients

	Total n = 231
Sex, males, n (%)	158 (68.4)
Age, median [IQR]	72 [64, 80]
Admission source, n (%)	
Hospital ward	56 (24.2)
Emergency department	106 (45.9)
Elective surgery	39 (16.9)
Emergency surgery	30 (13.0)
Charlson comorbidity index, median [IQR]	2 [1, 3]
Serum albumin, median [IQR], g/dL	2.80 [2.20, 3.20]
SOFA score*, median [IQR]	9 [6, 12]
APACHE II score*, median [IQR]	21 [14, 28]
SAPS II score*, median [IQR]	48 [37, 60]
ARDS, n (%)	42 (18.2)
Sepsis, n (%)	121 (52.4)
Acute kidney injury, n (%)	105 (41.1)
Renal replacement therapy, n (%)	58 (25.1)
Mechanical ventilation, n (%)	147 (63.6)
Noradrenaline, n (%)	139 (60.2)
Proton pump inhibitor, n (%)	196 (84.8)
Laxative drug, n (%)	119 (51.5)
Antibiotics, n (%)	214 (92.6)
Antiviral, n (%)	18 (7.8)
Chemotherapy, n (%)	8 (3.5)
Enteral nutrition, n (%)	157 (68.0)
<i>Clostridium difficile</i> infection [†] , n (%)	2 (0.9)
Cytomegalovirus enteritis, n (%)	2 (0.9)

	Total n = 231
Quantity of diarrhea, median [IQR], g	401 [230, 645]
Onset of diarrhea [‡] , median [IQR], day	3 [2, 6]
<p>*Three missing data</p> <p>†Defined by glutamate dehydrogenase positivity and <i>Clostridium difficile</i> toxin positivity.</p> <p>‡Number of days from ICU admission to the onset of diarrhea</p> <p>IQR: Interquartile range, SOFA: Sequential organ dysfunction assessment, ARDS: Acute respiratory distress syndrome, APACHE II: Acute Physiology and Chronic Health Disease Classification System, SAPS II: Simplified acute physiology score.</p>	

Association between the quantity of diarrhea and outcomes

Table 2 presents the primary and secondary outcomes. Two and 16 patients were lost to 28-day and 90-day follow-ups, respectively. In the unadjusted analysis, the quantity of diarrhea was associated with increased in-hospital mortality (unadjusted RR per 200 g increased: 1.10 [95% CI 1.01–1.19], $p = 0.03$). After adjusting for CCI, SOFA score, and serum albumin level, this association remained (adjusted RR per 200-g increase: 1.10 [95% CI 1.01–1.20], $p = 0.03$) (Table 3).

Table 2
Summary of primary and secondary outcomes

	Total n = 231
Primary outcome	
Hospital mortality, n/total n (%)	53/231 (22.9)
Secondary outcomes	
ICU mortality, n/total n (%)	21/231 (9.1)
28-day mortality*, n/total n (%)	35/229 (15.3)
90-day mortality [†] , n/total n (%)	52/215 (24.2)
ICU LOS, median [IQR], day	7.0 [4.0, 12.4]
ICU-free day survival at 28*, median [IQR], day	20.0 [14.0, 23.0]
Hospital LOS, median [IQR], day	35.0 [18.4, 58.0]
Hospital-free day survival at 90 [†] , median [IQR], day	45.0 [0, 66.5]
<p>*Two patients lost to follow-up, †16 patients lost to follow-up. There were no missing measurements in other outcomes. IQR: Interquartile range, LOS: Length of stay, IQR: Interquartile range, LOS: Length of stay</p>	

Table 3
Association between the quantity of diarrhea and in-hospital mortality

	Unadjusted		Adjusted	
	RR [95% CI]	p-value	RR [95% CI]	p-value
Primary analysis (per 200-g diarrhea increase)	1.10 [1.01, 1.19]	0.031	1.10 [1.01, 1.20]	0.029
Sensitivity analyses (per 200-g diarrhea increase)				
Model 1			1.09 [0.98, 1.20]	0.080
Model 2			1.10 [1.01, 1.20]	0.028
Model 3			1.11 [1.02, 1.22]	0.018
Model 4			1.10 [1.00, 1.20]	0.041
Complete case analysis	1.10 [1.05, 1.15]	0.001>	1.10 [1.04, 1.17]	0.002
Exclude CDI or CMV diagnosed in ICU	1.10 [1.03, 1.17]	0.006	1.14 [1.04, 1.24]	0.004
Quantile-defined categories				
Mild (< 250 g)	1.00 (reference)		1.00 (reference)	
Moderate (250–399 g)	0.97 [0.38, 2.49]	0.953	1.02 [0.51, 2.04]	0.963
Severe (400–649 g)	1.11 [0.46, 2.68]	0.823	1.29 [0.69, 2.43]	0.421
Very severe (≥ 650 g)	1.61 [0.85, 3.04]	0.145	1.77 [0.99, 3.21]	0.056
Primary model: CCI, SOFA score, and serum albumin, Model 1: age, sex, CCI without age score, SOFA score, and serum albumin. Model 2: CCI, APACHE II score, and serum albumin. Model 3: CCI, SAPS II score, and serum albumin. Model 4: CCI, SOFA score, serum albumin, and enteral nutrition RR: Risk ratio, CI: Confidence interval, CCI: Charlson comorbidity index, SOFA: Sequential Organ Failure Assessment, CDI: <i>Clostridium difficile</i> infection, CMV: Cytomegalovirus enteritis				

Sensitivity analyses for the primary analysis

The association between the quantity of diarrhea and in-hospital mortality remained similar in various multivariable analysis models and other sensitivity analyses (Table 3). We also performed a sensitivity analysis using the categories of the quantity of diarrhea. With no established criteria to distinguish the quantity of diarrhea, we used near-quantile-defined categories of the quantity of diarrhea. The quartiles of diarrhea were 230 g in the 25th percentile, 401 g in the 50th percentile, and 645 g in the 75th percentile. Therefore, the patients were divided into the following categories: mild (< 250 g), moderate (250–399 g), severe (400–649 g), and very severe ($\geq$ 650 g). In-hospital mortality was 19.7% (12/61) for mild, 19.2% (10/52) for moderate, 21.3% (13/61) for severe, and 31.6% (18/57) for very severe. Multivariable-modified Poisson regression analysis using these categories, with the same adjustments as in the primary model, showed a trend toward increased in-hospital mortality as the quantity of diarrhea increased (Table 3).

Secondary analyses

For secondary analyses, a similar association was observed between the quantity of diarrhea and ICU 28-day and 90-day mortalities (Table 4). Multivariable analysis showed a similar trend of higher mortality with higher quantities of diarrhea.

Table 4
Association between 200-g increase in the quantity of diarrhea and secondary outcomes

	Unadjusted		Adjusted	
	RR [95% CI]	p-value	RR [95% CI]	p-value
ICU mortality	1.17 [1.07, 1.29]	0.001	1.20 [1.07, 1.35]	0.002
28-day mortality	1.11 [1.01, 1.23]	0.028	1.11 [0.99, 1.23]	0.053
90-day mortality	1.10 [1.01, 1.19]	0.028	1.11 [1.01, 1.21]	0.025
All analyses were adjusted for CCI, SOFA score, and serum albumin level.				
RR: Risk ratio, CI: Confidence interval, CCI: Charlson comorbidity index, SOFA: Sequential Organ Failure Assessment				

Discussion

In this retrospective study, we investigated the association between the quantity of diarrhea and in-hospital mortality in 231 patients with newly developed diarrhea in the ICU. Multivariable analysis revealed that diarrhea quantity was an independent predictor of in-hospital mortality. This association was consistent across several sensitivity analyses. Similarly, the greater the quantity of diarrhea, the higher the ICU 28-day and 90-day mortalities. To the best of our knowledge, this is the first study to show an association between the quantity of diarrhea and mortality.

Previous studies have reported an association between the presence of diarrhea and mortality; however, no studies have examined whether mortality increases with a greater quantity of diarrhea [14, 42]. A systematic review of 12 studies, most of which used the definition of diarrhea as three or more loose or

liquid stools, showed an association between diarrhea and mortality (RR: 1.43; 95% CI: 1.03–1.98; $I^2 = 86.7\%$; $n = 11,866$) [14]. We focused on the quantity of diarrhea in this study and showed that mortality increased with increasing quantity of diarrhea according to the adjusted RR in patients with newly developed diarrhea in the ICU. More diarrhea leads to worse electrolyte imbalance, nutritional deficit, and hemodynamic instability owing to water loss [17, 18]. Clinicians need to correct electrolytes, adjust enteral nutrition, and increase fluid administration as diarrhea increases.

The reason for the higher mortality rate among patients with a greater quantity of diarrhea remains unclear. Patients with CDI or cytomegalovirus enteritis, which are common diseases causing diarrhea, have been reported to have higher mortality, but they were excluded from our study. Indeed, diarrhea can cause dehydration, electrolyte abnormalities, metabolic acidosis, malnutrition, device contamination, and wound contamination [1]. However, since dehydration and electrolyte abnormalities are carefully corrected in the ICU, it is questionable to assume that diarrhea directly contributes to mortality.

Possible explanations for the relationship between diarrhea and mortality are as follows. First, diarrhea can be a sign of gastrointestinal organ failure that is associated with a high risk of mortality [4, 14, 43]. Patients with diarrhea have higher severity scores than those without diarrhea [2, 6, 8–10, 14]. In our study, most patients received treatments that could cause diarrhea, such as enteral nutrition and antimicrobials. These interventions are part of the treatment regimen for critically ill patients. In addition, approximately 60% of patients were on ventilation and used vasopressors, which means that patients with diarrhea have a higher severity of illness. In our analysis, we adjusted for the SOFA score, an organ disorder score that does not include gastrointestinal function and showed that diarrhea is a risk factor for mortality independent of other organ disorders. The quantity of diarrhea may be a candidate when adjusting for organ dysfunction. Second, diarrhea can be a sign of a disorder of the gut microbiota, which is called dysbiosis. This dysbiosis is believed to increase vulnerability to nosocomial infections, sepsis, organ failure, and mortality [44, 45]. The development of diarrhea might be associated with dysbiosis in the gut microbiota of ICU patients [46]. However, our data and analyses are not sufficiently conclusive to prove them. Further research is needed to test these hypotheses.

This study had several limitations. First, the measurement of diarrhea was not completely accurate. If diarrhea spills out of the diaper, it may not be measured. In this case, this may have led to an underestimation of the quantity of diarrhea. However, we believe that this measurement of the quantity of diarrhea reflects real clinical practice. Second, the inter-rater reliability of BSCS was not confirmed in our study. The reliability of BSCS has been studied and widely used [26–32], and our nurses were trained to measure BSCS in clinical practice, which should have minimized the inter-rater variability. Third, we did not obtain information on urinary catheter insertion. However, we expect that most patients in this study had urinary catheters because only critically ill patients were admitted to our ICU (a median SOFA score of 9 and 63.6% of them were on ventilators). Finally, this was a single-center study, and the generalizability of the results is limited.

Conclusions

In ICU patients with newly developed diarrhea, greater quantity of diarrhea was associated with higher mortality. The quantity of diarrhea may be considered an indicator of disease severity in ICU patients. Further research is needed to determine if there is a causal relationship between the quantity of diarrhea and death.

Abbreviations

ICU

Intensive care unit

RR

Risk ratio

IQR

Interquartile range

CI

Confidence interval

ESICM

European Society of Intensive Care Medicine

CDI

Clostridium difficile infection

CMV

Cytomegalovirus

STROBE

Strengthening the Reporting of Observational studies in Epidemiology

WHO

World Health Organization

BSCS

Bristol stool chart scale

CCI

Charlson Comorbidity Index

APACHE

Acute Physiology and Chronic Health Evaluation

SAPS

Simplified Acute Physiology Score

SOFA

Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

This study was approved, and the need for informed consent was waived by the institutional review boards of the participating hospital.

Consent for publication

Not applicable.

Availability of data and materials

The dataset of this study is not publicly available based on the decision of the first author.

Competing interests

All authors have no conflicts of interest to declare.

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Authors' contributions

RY has complete access to the study data and takes responsibility for the data integrity. All authors contributed to the study concept and design. RY and YU contributed to data acquisition. RY and RU contributed to data analysis and interpretation. RY, RU, and HY drafted the manuscript. All authors are responsible for the critical revision of the manuscript for important intellectual content and have approved the final manuscript.

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Figures

Figure 1

Flow diagram