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ORIGINAL ARTICLE

Observational Study

Gastrointestinal manifestations of critical ill heatstroke patients and their associations with outcomes: A multicentre, retrospective, observational study

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Abstract

BACKGROUND

Extreme heat exposure is a growing health problem, and the effects of heat on the gastrointestinal (GI) tract is unknown. This study aimed to assess the incidence of GI symptoms associated with heatstroke and its impact on outcomes.

AIM

To assess the incidence of GI symptoms associated with heatstroke and its impact on outcomes.

METHODS

Patients admitted to the intensive care unit (ICU) due to heatstroke were included from 83 centres. Patient history, laboratory results, and clinically relevant outcomes were recorded at ICU admission and daily until up to day 15, ICU discharge, or death. GI symptoms, including nausea/vomiting, diarrhoea, flatulence, and bloody stools, were recorded. The characteristics of patients with heatstroke concomitant with GI symptoms were described. Multivariable regression analyses were performed to determine significant predictors of GI symptoms.

RESULTS

A total of 713 patients were included in the final analysis, of whom 132 (18.5%) patients had at least one GI symptom during their ICU stay, while 26 (3.6%) suffered from more than one symptom. Patients with GI symptoms had a significantly higher ICU stay compared with those without. The mortality of patients who had two or more GI symptoms simultaneously was significantly higher than that in those with one GI symptom. Multivariable logistic regression analysis revealed that older patients with a lower GCS score on admission were more likely to experience GI symptoms.

CONCLUSION

The GI manifestations of heatstroke are common and appear to impact clinically relevant hospitalization outcomes.

Key Words: Extreme heat; Flatulence; Sunstroke; Intensive care units; Diarrhea

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Core Tip: This study aimed to assess the incidence of gastrointestinal (GI) symptoms associated with heatstroke and its impact on outcomes. This was a retrospective, multi-center, observational cohort study that involved patients admitted to 83 intensive care unit located in 16 cities in the Sichuan Province, China between June 1 and October 31, 2022. Results showed older heatstroke patients with a lower Glasgow coma scale score on admission were more likely to experience GI symptoms, which had statistical difference. Clinicians should pay attention to the time at which heatstroke patients started manifesting GI symptoms, as well as the duration of said symptoms, to ensure that patients are timely treated with the proper enteral therapy and have the best prognosis possible.

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INTRODUCTION

Owing to the effects of climate change, extreme heat is rapidly becoming a global public health concern. Direct exposure to extreme heat can cause dysregulation of body temperature, leading to heatstroke[1]. Over the past two decades, there has been a 50% increase in heat-related mortality among adults aged 65 and older. As an acute life-threatening condition manifesting an uncontrolled rise in core body temperature, heatstroke presents clinically as a systemic disorder and comprises the following symptoms: Encephalopathy, hypotension, respiratory failure, liver, muscle, coagulopathy and kidney damage[2]. In recent years, some studies have indicated that sustained high body temperature can cause structural and functional damage to the gastrointestinal (GI) tract, resulting in vomiting, diarrhoea, or intolerance to enteral nutrition (EN), which can exacerbate patients' condition[3,4]. Nevertheless, the impact of heatstroke on the GI tract remains to be elucidated.

Located in southwestern part of China, the Sichuan Province is the second largest Chinese province, with a permanent population of more than 80 million. According to the records of the Sichuan meteorological administration, as of May 2022, summer temperatures have reached a historical high since 1961, with two consecutive strong high-temperature periods. One of the most notable consequences of this phenomenon is the significant increase in the number of cases of heatstroke. Accordingly, we conducted a retrospective, multi-center study to examine the demographic characteristics of heatstroke patients admitted to the intensive care unit (ICU) in 2022. Our study primarily aimed to determine the incidence of GI disturbances among patients experiencing heatstroke from various medical centres in the Sichuan Province, with a secondary objective of identifying the risk factors for GI symptoms after heatstroke.

MATERIALS AND METHODS

This was a retrospective, multi-center, observational cohort study that involved patients admitted to 83 ICUs located in 16 cities in the Sichuan Province, China between June 1 and October 31, 2022. Ethical approval for this study was obtained from the Biomedical Ethics Review Committee of the West China Hospital of Sichuan University (approval No. SCU-2022-1542), in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of this study, the requirement for informed consent was waived.

Patients and examination

Inclusion criteria comprised: (1) an age > 18 years; and (2) hospitalization in any type of ICU due to heatstroke or heatstroke-related complications. Patients with heatstroke were diagnosed by front-line medical staff in each center, and the diagnosis was made according to the corresponding clinical manifestations, as well as clinical history[5]. The exclusion criteria included an age < 18; burns; death within 24 h following ICU admission; palliative care; and simultaneous participation in any other nutrition-related interventional studies. Patients whose data is unsuitable for the analysis performed in this study were also excluded. Demographic characteristics were recorded at ICU admission, and clinical variables were recorded daily until up to day 15 of ICU stay or ICU discharge or death. Patients included in the study were managed by physicians in their respective ICUs. The treatment plan for each patient was determined by the attending physician based on the patient's individual condition.

Data collection and definitions

An electronic data capture system (Sichuan Zhikang Technology Co., Ltd, China) was implemented to gather information on heatstroke patients. Data collectors, who were primarily front-line physicians in each centre's ICU, recorded information on each patient. The data collected was determined after extensive discussion based on expert opinions and in combination with literature review. The trial filling of data was conducted twice through two extensive online meetings with experts from each center to finalize all forms. A training in which the use of the electronic data capture system and heatstroke-related knowledge are explained was conducted in each center before initiating data collection. An online meeting would be hosted every week to check the quality of the data collected during said week. The data underwent a two-step verification process to ensure its completeness and accuracy, and unqualified data was to be collected again. Four researchers (Yu-Cong Wang, Lie-Tao Wang, Lv-Yuan Shi, and Ding-Yuan Wan) reviewed all data independently for completeness and accuracy, and the data management team (Min He, Jing Yang and Qin Wu) conducted a thorough cleaning of the data, identifying any missing information.

Data comprising baseline information, laboratory test results, treatment plan, GI symptoms, nutrition support, and patient outcome were collected in the electronic data capture system. As demographic information, age, sex, body mass index (BMI), and concomitant diseases were collected. Patients' body temperature at hospital admission, including duration of exposure to heat, first symptoms according to chief complain, nutrition risk screening 2002 (NRS-2002), and Glasgow coma scale (GCS) score were also recorded. Moreover, the average, maximum, and minimum temperature data for the months of May, June, and July in 2022, which was publicly available on the website of the Sichuan meteorological administration, was also collected. The definition of fever in this study was set as a body temperature greater than 37.3 °C as determined through anal temperature measurement. High environment temperature was defined as when the maximum environment temperature reaches or exceeds 35 °C. If the high temperature lasts for more than 3 d, it was defined as a high temperature heat wave. Treatment received during the observation period, including organ support technical, antibiotics, and steroids, were recorded.

GI symptoms were defined as the presence of nausea/vomiting, diarrhoea, flatulence, or bloody stools that do not resolve with medical therapy[6-8]. Specifically, nausea/vomiting in non-intubated patients was defined as the self-reporting of epigastric discomfort followed by vomiting, self-reporting of nausea alone without vomiting, or vomiting alone without nausea. As for intubated patients, nausea/vomiting was defined as the presence of reflux or aspiration for abnormal causes. Diarrhoea was defined as frequent exclusion of loose thin faeces or even watery stools for more than 3 times daily of more than 200 mL each time. Flatulence was defined as awake patients feeling fullness in part or all of the abdomen or partial or total abdominal distention as determined by physical examination in non-awake patients. Bloody stool was defined as having a positive faecal occult blood test more than twice or dark red or black stool. Information on GI symptoms comes from the hourly nursing observation records or daily disease course records.

For patients' outcome, we collected complications during the observational period, mortality at 15 d, and length of stay in the ICU. The complications in this study included disturbance of water and electrolyte, rhabdomyolysis, myocardial damage, acute kidney injury, acute liver function impairment, and central nervous system impairment. More specifically, disturbance of water and electrolyte was defined as dehydration, oedema, hyperkalaemia, hypokalemia, hypercalcemia, hypocalcaemia, hypermagnesemia or hypomagnesemia, as determined by clinicians. Rhabdomyolysis was defined as muscle pain, tenderness, swelling, weakness, and other muscle involvement and serum creatine kinase levels being significantly elevated more than 5 times the upper limit of normal. Myocardial damage was defined as elevated myocardial enzymes with a normal electrocardiogram. Acute kidney injury was defined according to the kidney disease: Improving Global Outcomes criteria after high temperature exposure. Acute liver function impairment was defined as elevated serum aminotransferase and bilirubin levels above the normal limit after exposure to high temperature with the absence of chronic liver disease, liver failure, coagulation dysfunction, and hepatic encephalopathy. Central nervous system impairment was defined as the occurrence of seizures, motor dysfunction, or sensory dysfunction, including limb hemiplegia, immobility, numbness of the hemi limb, or spontaneous pain in a patient with no history of central nervous system disease.

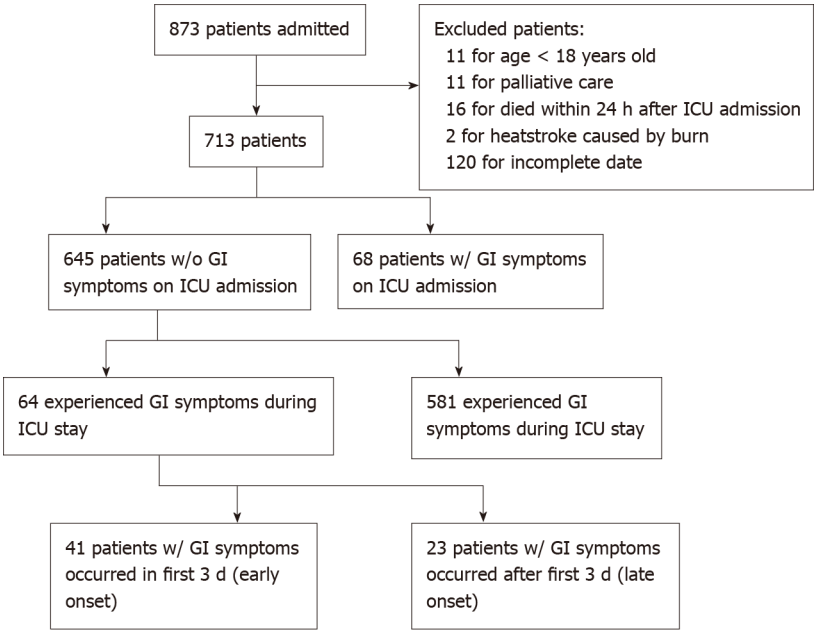

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Figure 1 Flow chart of the study. Patients were grouped according to whether gastrointestinal (GI) symptoms occurred on intensive care unit (ICU) admission, then whether GI symptoms occurred during ICU hospitalization and the onset of patients' GI symptoms. ICU: Intensive care unit; GI: Gastrointestinal; w: With; o: Without.

The primary outcome of the study was the incidence of post-heatstroke GI symptoms, as determined through data collection by trained data collectors. Secondary outcomes included the identification of risk factors for GI dysfunction following heatstroke.

Statistical analysis

Statistical analysis was performed using descriptive statistics. Continuous variables were reported as median and quartile ranges or simple ranges, while categorical variables were summarized as counts and percentages. Items missing more than 10% of their data will be excluded from the analysis, and no imputation was made for missing data. All data were analysed using SPSS Statistics version 25 software (IBM Corp., Armonk, NY, United States). Descriptive statistical analyses reflected the distribution of characteristics of the sample population across case and control groups in the form of counts and proportions. *T* tests and χ^2 tests were applied to test the association between case and control group variables. The incidence of confirmed cases was visually represented using a map created with Dychart.com (Wuhan Dysprosium Metadata Technology Co., Ltd, Wuhan, Hubei, China). We developed a logistic regression model to assess the association between the rates of GI dysfunction after heatstroke and several high-risk indicators, including age, initial temperature, initial symptoms, and comorbidities using Graphpad Prism 9 XML project (Graphpad Software Inc., San Diego, CA, United States).

RESULTS

Study population

Between June 1, 2022 and October 31, 2022, a total of 873 patients admitted from 83 ICUs across 16 cities due to heatstroke were collected. Of these patients, 160 were excluded as follows: 11 patients were excluded as they were under 18 of age; 2 for heatstroke caused by burn; 16 for mortality within 24 h after ICU admission; 11 for palliative care after ICU admission; and 120 for incomplete data (Figure 1). A total of 713 patients were enrolled in the final analysis. The number of patients enrolled each day during the trial period and daily change in average and maximum temperature in the Sichuan Province are displayed in Supplementary Figure 1. The number of centres from different cities participating in the trial and corresponding total number of patients enrolled are shown in Supplementary Figure 2.

Of the 713 analysed patients, 46.6% were female, and the median age was 72 years [interquartile range (IQR): 64–80; Table 1]. The median body temperature of patients at hospital admission was 40.7 (IQR: 40.0 to 41.3). Around 50% of patients (343/713, 48.10%) were admitted with altered mental states or behaviours. Part of the cohort had at least one underlying illness, such as hypertension (187/713, 26.20%) or diabetes (87/713, 12.20%). Upon admission, the median level of C-reactive protein was elevated (5.0 mg/L, IQR: 1.0–11.8). The same was true for the median levels of procalcitonin (2.7 mg/mL, IQR: 0.5–13.1), and median D-dimer (4.6 mg/L, IQR: 1.8–12.9). A total of 439 patients (61.7%) underwent endotracheal intubation upon ICU admission. At day 15, 349 patients (48.9%) were discharged from the hospital, while 144 (20.2%) died, 187 (26.2%) were still hospitalized, and 33 (4.6%) transferred to another hospital. During

Table 1 Clinical characteristics, laboratory findings at admission, gastrointestinal symptoms findings, complications, treatments, and clinical outcomes of the study patients, according to developed gastrointestinal symptoms or not[1]

	All Patients, (*n* = 713)	GI Symptoms whether[2]		*P* value
		Yes (*n* = 132)	No (*n* = 581)	
Characteristic				
Age, median (IQR), yr	72.0 (64.0-80.0)	70.0 (59.0-76.0)	73.0 (64.0-81.0)	0.076
Distribution, *n* (%)				
0-39 yr	13 (1.8)	1 (0.01)	12 (2.1)	–
40-59 yr	132 (18.5)	32 (24.2)	100 (17.2)	–
60-79 yr	371 (52.0)	73 (55.3)	298 (51.2)	–
≥ 80 yr	197 (27.6)	26 (19.6)	171 (29.4)	–
Female sex	332 (46.6)	60 (45.4)	272 (46.8)	0.561
BMI, median (IQR), kg/m^2	22.1 (20.3-24.2)	22.5 (20.0-24.6)	22.0 (20.3-24.1)	0.875
GCS score at ICU admission, median (IQR)	6.0 (4.0-9.0)	5.0 (3.0-7.0)	6.0 (4.0-9.0)	0.018
NRS-2002 score at ICU admission, median (IQR)	4.0 (3.0-5.0)	3.0 (3.0-5.0)	4.0 (3.0-5.0)	0.014
Body temperature on admission				
Patients, *n* (%)	710 (99.1)	132 (100.0)	578 (98.8)	0.374
Temperature, median (IQR), °C	40.7 (40.0-41.3)	41.0 (40.1-42.0)	40.5 (40.0-41.2)	< 0.001
Heat exposure duration, median (IQR), h	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.3)	0.206
Distribution of body temperature on admission, *n* (%)				
< 37.3 °C	6 (1.0)	0 (0.0)	6 (0.1)	–
37.3–38.0 °C	13 (2.1)	1 (0.8)	12 (2.3)	–
38.1–39.0 °C	59 (9.3)	8 (6.7)	51 (9.9)	–
39.1–40.0 °C	175 (27.7)	33 (27.7)	142 (27.7)	–
> 40.0 °C	379 (60.0)	77 (64.7)	302 (58.9)	–
Number of complaints and symptoms on admission, *n* (%)				
< 2	169/672 (25.1)	27/126 (21.4)	142/546 (26.3)	0.053
2-3	348/672 (51.8)	47/126 (37.3)	301/546 (55.1)	0.094
> 3	155/672 (23.1)	52/126 (41.3)	103/546 (18.9)	< 0.001
Complaints and symptoms on admission, *n* (%)				
Fever	476 (66.8)	93 (70.5)	383 (65.9	0.272
Altered mental state or behavior	343 (48.1)	55 (41.7)	288 (49.6	0.177
Dry skin or excessive sweating	65 (9.1)	20 (15.1)	45 (7.7)	< 0.001
Rubefaction	32 (4.5)	11 (8.3)	21 (3.6)	0.035
Fast pulse	142 (19.9)	40 (30.3)	102 (17.5	< 0.001
Polypnea	175 (24.5)	38 (38.7)	137 (23.6)	0.019
Headache	15 (2.1)	3 (2.3)	12 (2.1)	0.438
Syncope	309 (43.3)	85 (64.4)	224 (38.6)	< 0.001
Other	102 (14.3)	27 (20.5)	75 (12.9)	0.013
Coexisting disorder, *n* (%)				
Diabetes	87 (12.2)	10 (7.6)	77 (13.3)	0.225
Hypertension	187 (26.2)	36 (27.3)	151 (26.0)	0.985

Chronic obstructive pulmonary disease	124 (17.4)	21 (15.9)	103 (17.7)	0.697
Chronic cardiac insufficiency	79 (11.1)	16 (12.1)	63 (10.8)	0.541
Hepatitis B infection	14 (2.0)	1 (0.8)	13 (2.2)	0.488
Cancer[3]	5 (0.7)	3 (2.3)	2 (0.3)	0.033
Chronic renal disease	17 (2.4)	2 (1.5)	15 (2.6)	0.149
Immunodeficiency	9 (1.3)	3 (2.3)	6 (1.0)	0.965
Laboratory findings, median (IQR)				
PaO_2/FiO_2 ratio	239.0 (174.0-323.0)	238.0 (185.5-300.5)	248.0 (190.0-336.0)	0.064
White-cell count, 10^9/L	11.7 (8.2-15.5	10.0 (6.6-14.4),	11.7 (8.4-15.5)	0.032
Lymphocyte count, 10^9/L	1.3 (0.7-2.4)	0.9 (0.5-2.3)	1.0 (0.6-2.1)	0.746
Platelet count, 10^9/L	108.0 (73.0-162.0)	84.0 (45.0-115.0)	110.0 (75.0-165.5)	0.147
Hemoglobin, g/L	123 (109-138)	115 (102-127)	124 (109-138)	0.014
Albumin, g/L	37.0 (33.2-40.2)	33.4 (29.1-43.8)	37.0 (33.3-40.3)	0.014
Other findings, median (IQR)				
C-reactive protein, mg/L	5.0 (1.0-11.8)	11.9 (5.1-32.1)	5.0 (1.0-12.0)	0.005
Procalcitonin, ng/mL	2.7 (0.5-13.1)	3.2 (0.4-8.9)	2.8 (0.5-12.6)	0.593
Lactate dehydrogenase, U/L	367.9 (284.8-547.5)	327.0 (273.0-507.4)	362.5 (281.8-524.0)	0.667
Aspartate aminotransferase, U/L	79.0 (40.9-191.0)	115.9 (51.3-269.8)	74.0 (39.3-168.8)	0.128
Alanine aminotransferase, U/L	38.0 (21.0-85.0)	48.0 (28.1-104.1)	36.0 (20.0-77.3)	0.479
Total bilirubin, μmol/L	17.9 (12.5-25.7)	18.2 (11.8-258.9),	17.9 (12.5-25.9)	0.186
CK-Mb, U/L	10.0 (2.8-32.0)	13.6 (4.2-74.6)	9.9 (2.7-31.7)	0.539
Creatinine, μmol/L	125.0 (89.8-169.2)	122.0 (84.0-162.	123.0 (88.4-169.2)	0.944
D-dimer, mg/L	4.6 (1.8-12.9)	4.1 (2.1-8.6)	4.7 (1.7-12.8)	0.561
Minerals, median (IQR), mmol/L				
Sodium	133.3 (129.0-139.0)	136.0 (132.0-140.0)	133.6 (129.0-139.0)	0.158
Potassium	3.2 (2.9-3.8)	3.6 (3.0-3.9)	3.2 (2.9-3.8)	0.043
Lactate	3.5 (2.1-5.1)	3.1 (1.6-4.1)	3.4 (2.0-5.1)	0.036
GI symptoms findings, *n* (%)				
Duration of GI symptoms, median (IQR), d	–	4.0 (2.0-7.0)	–	–
Diarrhea	–	99 (75.0)	–	–
Flatulence	–	36 (27.3)	–	–
Nausea/vomiting	–	21 (15.9)	–	–
Bloody stools	–	8 (6.1)	–	–
Complications, *n* (%)				
Number of complications				
< 2	263 (36.9)	28 (21.1)	235 (38.8)	0.002
2-3	133 (18.7)	12 (9.2)	121 (19.8)	0.025
> 3	317 (44.5)	92 (69.7)	225 (41.4)	< 0.001
Disturbance of water and electrolyte	412 (57.8)	95 (72.0)	317 (54.6)	0.013
Rhabdomyolysis	102 (14.3)	34 (25.8)	68 (11.7)	0.004
Myocardial damage	281 (39.4)	70 (53.0)	211 (36.3)	< 0.001
Disseminated intravascular coagulation	221 (31.0)	62 (46.9)	159 (27.4)	0.006
Acute respiratory distress syndrome	256 (35.9)	66 (50.0)	190 (32.7)	0.001

Acute kidney injury	299 (41.9)	83 (62.9)	216 (37.2)	0.003
Acute liver function impairment	305 (42.8)	81 (61.4)	224 (38.6)	< 0.001
Central nervous system damage	256 (35.9)	74 (56.1)	182 (31.9)	0.003
Treatments, *n* (%)				
Mechanical ventilation				
Invasive	439 (61.7)	108 (82.6)	331 (57.1)	< 0.001
Noninvasive	10 (1.4)	0 (0.0)	10 (1.6)	0.271
Use of continuous renal-replacement therapy	24 (3.4)	7 (9.2)	17 (2.7)	0.003
Length of ICU stay, median (IQR), d	2.0 (1.0-4.0)	4.0 (2.0-7.0)	2.0 (1.0-3.0)	0.001
Clinical outcomes at data cutoff, *n* (%)				
Hospital discharge	349 (48.9)	64 (48.5)	285 (49.1)	0.906
Death	144 (20.2)	26 (19.7)	118 (20.3)	0.874
Still hospitalization	187 (26.2)	33 (25.0)	154 (26.5)	0.723
Transferred to another hospital	33 (4.6)	9 (6.8)	24 (4.1)	< 0.001

[1]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
[2]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
[3]Included in this category is any type of cancer.
IQR: Interquartile range; GCS: Glasgow coma scale; NRS: Nutrition risk screening; GI: Gastrointestinal; BMI: Body mass index; ICU: Intensive care unit; CK-Mb: Creatine kinase.

hospitalization, acute liver dysfunction was observed in 42.8% (305/713) patients, 41.9% (299/713) experienced acute kidney injury, 39.4% (281/713) experienced myocardial damage, and 35.9% (256/713) experienced central nervous system damage.

Patient characteristics and outcomes according to whether gastrointestinal symptoms are present

Our study results showed that 18.5% (132/713) of heatstroke patients experienced at least one episode of GI symptoms during ICU stay. Of these patients, 8 (6.1%) experienced bloody stools, 21 (15.9%) experienced nausea/vomiting, 36 (27.3%) experienced flatulence, and 99 (75.0%) experienced diarrhoea (Table 1 and Figure 2). Patients with heatstroke were subsequently categorized into two groups: Those who experienced GI symptoms (n = 132) and those who did not (n = 581) during their ICU stay. There was no difference in the median age of patients between both groups (Table 1). Patients with GI symptoms had significantly lower GCS scores (5.0 *vs* 6.0, ^{a}P = 0.018) and lower NRS-2002 scores (3.0 *vs* 4.0, ^{b}P = 0.014) on admission. There was also no significant difference in the presence of comorbidities upon admission between the groups during the study period, except for a prior history of cancer (2.5% *vs* 0.5%, ^{c}P = 0.033; Table 1). Laboratory results on admission revealed that patients with GI symptoms had significantly lower levels of albumin (33.4 *vs* 37.0, ^{d}P = 0.014) and hemoglobin (115.0 *vs* 124.0, ^{e}P = 0.014) and a higher level of blood lactate (3.1 *vs* 3.4, ^{e}P = 0.036) and C-reactive protein (11.9 *vs* 5.0, ^{f}P = 0.043). It was observed that patients presenting with GI symptoms had an increased likelihood of developing multiple complications, including acute kidney injury (62.9%, ^{g}P = 0.003), acute liver function impairment (61.4%, ^{h}P < 0.001), and central nervous system damage (56.1%, ^{i}P = 0.003). However, the presence of GI symptoms did not have a significant impact on patient mortality. Multivariate logistic regression showed that heatstroke patients who were older than the average year of the cohort were more likely to develop GI symptoms (^{j}P = 0.001; Figure 3A). Moreover, patients with a lower GCS score were prone to have GI symptoms (^{k}P = 0.006; Figure 3A). This positive correlation of GCS score with GI symptoms persisted when we adjusted for complications (Figure 3B) and laboratory results (Figure 3C).

Relationship between GI symptoms and enteral nutrition therapy

Considering that the predominant GI symptom is diarrhoea, a total of 439 heatstroke patients with endotracheal intubation shortly after ICU admission were analysed to explore the relationship between GI symptoms and EN therapy. We found that the presence of GI symptoms was not associated with EN therapy (Table 2). There was no statistical difference in the proportion of EN support, amount of calories and proteins, and total volume received on admission between the patients who underwent EN therapy. Of note, EN therapy was initiated in only a small proportion (139/439, 31.7%) of intubated patients within 48 h after ICU admission, as shown in Table 3. Patients who did not start EN within 48 h of ICU admission had a significantly lower GCS score (5.0 *vs* 4.0, ^{l}P = 0.002), experienced more GI symptoms after ICU admission (22.3% *vs* 12.9%, ^{m}P = 0.021), and had a longer ICU stay (3.0 *vs* 2.0, ^{n}P < 0.001). Logistic regression analysis showed that GI symptoms were an independent risk factor for not initiating early EN (^{o}P = 0.037; Supplementary Figure 3). During the observational period, 266 (60.6%) patients with endotracheal intubation at admission failed

Table 2 Clinical characteristics of the heatstroke patients with endotracheal intubation, according to developed gastrointestinal symptoms or not[1]

	All intubated patients (*n* = 439)	GI symptoms whether[2]		*P* value
		Yes (*n* = 108)	No (*n* = 331)	
Characteristic				
Age, median (IQR), yr	71.0 (63.0-80.0)	72.0 (64.0-80.0)	69.5 (59.8-78.0)	0.202
Female sex, *n* (%)	197 (44.9)	49 (45.4)	148 (44.7)	0.905
GCS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	4.0 (4.0-5.0)	0.204
NRS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	3.0 (3.0-5.0)	4.0 (3.0-5.0)	0.057
Body temperature on admission				
Patients, *n* (%)	439 (100.0)	108 (100.0)	331 (100.0)	0.348
Temperature, median (IQR), °C	41.0 (40.0-41.8)	41.0 (40.0-42.0)	41.0 (40.0-41.6)	0.497
Complaints and symptoms on admission, *n* (%)				
Fever	296 (67.4)	76 (70.4)	220 (66.5)	0.452
Altered mental state or behavior	205 (46.7)	41 (38.0)	164 (49.5)	0.036
Dry skin or excessive sweating	45 (10.3	20 (18.5)	25 (7.6)	0.001
Rubefaction	17 (3.9)	9 (8.3)	8 (2.4)	0.006
Fast pulse	99 (22.6)	34 (31.5)	65 (19.6)	0.105
Polypnea	122 (27.8)	31 (28.7)	91 (27.5)	0.807
Headache	7 (1.6)	2 (18.5)	5 (1.5)	0.805
Syncope	207 (47.2)	70 (64.8)	137 (41.4)	< 0.001
Other	61 (13.9)	71 (65.7)	40 (12.1)	< 0.001
Laboratory findings, median (IQR)				
PaO_2/FiO_2 ratio	225.0 (135.5-306.5)	221.0 (148.7-308.0)	226.0 (155.0-305.5)	0.999
White-cell count, 10^9/L	11.7 (8.1-15.6)	11.8 (8.0-15.8)	11.7 (8.1-15.6)	0.405
Lymphocyte count, 10^9/L	1.7 (0.8-2.8)	1.6 (0.8-2.8)	1.8 (0.8-28)	0.279
Platelet count, 10^9/L	92.0 (56.0-138.0)	83.5 (55.5-114.5)	97.0 (59.0-141.0)	0.143
Hemoglobin, g/L	124.0 (109.0-139.0)	121.0 (108.3-135.8)	125.0 (110.0-139.0)	0.053
Albumin, g/L	35.3 (32.5-38.9)	34.5 (31.8-38.0)	35.3 (32.5-38.9)	0.028
EN support				
Early (< 48 h) EN, *n* (%)	68 (15.5)	13 (12.0)	55 (16.6)	0.253
Average EN calorie, median (IQR), kcal/d	1000.0 (750.0-1500.0)	1000.0 (750.0-1500.0)	1000.0 (750.0-1500.0)	0.559
Average EN protein, median (IQR), g/d	28.0 (17.0-56.0)	30.0 (17.0-56.0)	28.0 (20.0-56.0)	0.867
Average EN volume, median (IQR), mL/d	600.0 (150.0-1150.0)	625.0 (142.5-1200.0)	600.0 (150.0-1082.5)	0.31
Complications, *n* (%)				
Disturbance of water and electrolyte	271 (61.7)	89 (82.4)	187 (56.5)	< 0.001
Rhabdomyolysis	81 (18.5)	31 (28.7)	50 (15.1)	0.002
Myocardial damage	216 (49.2)	63 (58.0)	153 (46.2)	0.029
Disseminated intravascular coagulation	172 (39.2)	54 (50.0)	118 (35.6)	0.001
Acute respiratory distress syndrome	226 (51.5)	62 (57.4)	164 (49.5)	0.156
Acute kidney injury	233 (53.1)	77 (71.3)	156 (47.1)	< 0.001
Acute liver function impairment	332 (75.6)	73 (65.6)	159 (48.0)	< 0.001
Central nervous system damage	206 (46.9)	65 (60.2)	141 (42.6)	0.001

Clinical outcomes at data cutoff, *n* (%)				
Hospital discharge	210 (47.8)	51 (47.2)	159 (48.0)	0.234
Death	123 (28.0)	24 (22.2)	99 (29.9)	0.122
Still hospitalization	78 (17.8)	24 (22.2)	54 (16.3)	0.163
Transferred to another hospital	28 (6.4)	9 (8.3)	19 (5.7)	0.338

[1]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
[2]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range; GCS: Glasgow coma scale; NRS: Nutrition risk screening; GI: Gastrointestinal; EN: Enteral nutrition; ICU: Intensive care unit.

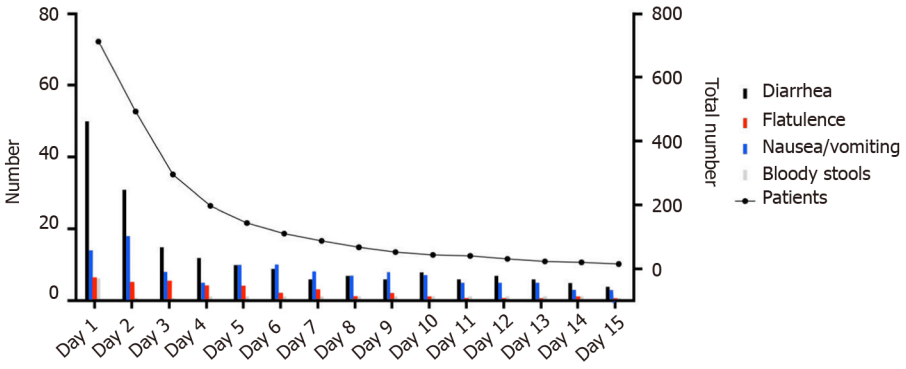

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Figure 2 Number of patients with gastrointestinal symptoms and total number of heatstroke patients still in the intensive care unit per day.

to establish full EN (Table 4). Patients who do not receive full EN experienced more GI symptoms (22.6% *vs* 14.5%, [p]*P* = 0.036). Moreover, the mortality of patients who did not receive full EN was significantly higher than those who did (35.3% *vs* 16.8%, [q]*P* < 0.001). Moreover, rhabdomyolysis (20.7% *vs* 11.6%, [r]*P* = 0.013) and acute kidney injury (57.9% *vs* 45.7%, [s]*P* = 0.012) were more common, and ICU stay was longer in the former population (3.0 *vs* 2.0, [t]*P* < 0.001).

Subgroup analysis

Since the definition of GI manifestations was composite, we subsequently explore whether there was difference in the characteristics of patients with different symptoms. We selected patients with a single symptom and divided them into 3 groups according to different GI manifestations (Table 5). There was a statistically significant difference in temperature on admission between patients with diarrhoea, flatulence, and nausea/vomiting ([u]*P* = 0.003). Notably, there were significant differences in complications between the three subgroups, except for complications of disturbance of water and electrolyte. Although mortality was not different between subgroups, the difference in the number of patients who were still hospitalized was statistically significant ([v]*P* = 0.025).

As we observed that the onset of GI symptoms was significantly different between patients, we further divided patients with GI symptoms into two categories: Those with GI symptoms on ICU admission and those with GI symptoms developed during ICU stay. The patient characteristics of both groups are shown in Table 6. The patients who had GI symptoms on admission were younger ([v]*P* = 0.050), had a higher BMI (22.7 *vs* 21.1, [w]*P* = 0.050), and had a lower nutrition risk screening (NRS-2002) score on admission (3.0 *vs* 4.0, [x]*P* = 0.009) than had those who developed symptoms later on. Patients who had less GI symptoms on admission had a lower number of comorbidities, including diabetes (1/68, 1.5% *vs* 9/64, 14.1%, [y]*P* = 0.009), but more complications, including haemorrhage of the digestive tract (23/68, 33.8% *vs* 12/64, 18.8%) and disseminated intravascular coagulation (38/68, 55.9% *vs* 24/64, 37.5%). Nevertheless, there is no difference in mortality and ICU length of stay.

We divided patients who developed GI symptoms during their ICU stay into the early-onset (< 3 d of ICU stay) and late-onset groups (≥ 3 d of ICU stay) groups. As shown in Table 7, there was a significant statistical difference in EN support between the two groups. Fewer patients received EN support in the early-onset than in the late-onset group (29/41, 70.7 *vs* 22/23, 95.7%, [z]*P* < 0.001). The early-onset group received less EN calorie [752.0 kcal/d (IQR: 500.0–1007.5) *vs* 1292.0 kcal/d (IQR: 750.0-1560.0)], protein [20.0 g/d (IQR: 17.6–32.5) *vs* 28.0 g/d (IQR: 15.0–57.0)], and EN volume [600.0 mL/d (IQR: 147.5–1000.0) *vs* 900.0 mL/d (IQR: 461.2–1500.0)]. Moreover, patients in the early-onset group received EN support for a shorter time than did those in the late-onset group [3.0 d (IQR: 1.8–5.0) *vs* 7.0 d (IQR: 4.0–11.0)].

To further explore the relationship between the duration of GI symptoms and prognosis of heatstroke patients, we stratified patients into those who had GI symptoms for more than 4 d and those who did for had GI symptoms for less than 4 d, as shown in Table 8. Patients with GI symptoms for at least 4 d had lower albumin levels (37.0 g/L *vs* 34.4 g/L,

Table 3 Characteristics of the heatstroke patients with endotracheal intubation, according to received enteral nutrition within 48 h after intensive care unit admission or not[1]

	All intubated patients (*n* = 439)	EN therapy whether ≤ 48 h		*P* value
		Yes (*n* = 139)	No (*n* = 300)	
Characteristic				
Age, median (IQR), yr	71.0 (63.0-80.0)	72.0 (63.0-80.0)	71.0 (63.0-79.0)	0.801
Female sex, *n* (%)	197 (44.9)	62 (46.8)	135 (43.6)	0.938
GCS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	5.0 (3.0-7.0)	4.0 (3.0-5 .0)	0.002
NRS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	5.0 (4.0-6.0)	4.0 (3.0-5.0)	0.017
Body temperature on admission				
Patients, *n* (%)	439 (100.0)	139 (100.0)	300 (100.0)	–
Temperature, median (IQR), °C	41.0 (40.0-41.8)	41.0 (40.0-41.5)	41.0 (40.0-42.0)	0.154
Laboratory findings, median (IQR)				
PaO_2/FiO_2 ratio	225.0 (135.5-306.5)	226.0 (164.0-287.0)	223.0 (128.0-316.0)	0.825
White-cell count, 10^9/L	11.7 (8.1-15.6)	12.4 (8.6-16.8)	11.3 (8.0-15.0)	0.290
Lymphocyte count, 10^9/L	1.7 (0.8-2.8)	1.5 (0.7-2.3)	1.9 (0.9-3.0)	0.105
Platelet count, 10^9/L	92.0 (56.0-138.0)	101.0 (66.8-147.3)	88.0 (54.0-130.0)	0.039
Hemoglobin, g/L	124.0 (109.0-139.0)	122.0 (109.0-136.0)	124.5 (109.0-140.0)	0.311
Albumin, g/L	35.3 (32.5-38.9)	35.1 (32.0-38.5)	35.4 (32.5-39.0)	0.544
GI symptoms[2], *n* (%)				
Total patients	85 (19.4)	18 (12.9)	67 (22.3)	0.021
Diarrhea	60 (13.7)	13 (9.4)	47 (15.7)	0.073
Flatulence	25 (5.7)	7 (5.0)	18 (6.0)	0.685
Nausea/vomiting	14 (3.2)	7 (5.0)	7 (2.3)	0.134
Bloody stools	8 (1.8)	0 (0.0)	8 (2.6)	0.052
Complications, *n* (%)				
Disturbance of water and electrolyte	271 (61.7)	79 (56.8)	192 (64.0)	0.151
Rhabdomyolysis	81 (18.5)	20 (11.6)	61 (20.3)	0.135
Myocardial damage	216 (49.2)	65 (46.8)	151 (50.3)	0.486
Disseminated intravascular coagulation	172 (39.2)	50 (36.0)	122 (40.7)	0.349
Acute respiratory distress syndrome	226 (51.5)	74 (53.2)	152 (50.7)	0.616
Acute kidney injury	233 (53.1)	66 (47.5)	167 (55.7)	0.110
Acute liver function impairment	332 (75.6)	74 (53.2)	258 (86.0)	< 0.001
Central nervous system damage	206 (46.9)	62 (44.6)	144 (48.0)	0.507
Treatments				
Use of continuous renal-replacement therapy, *n* (%)	34 (7.7)	10 (8.1)	20 (7.5)	0.826
Length of ICU stay, median (IQR), d	2.0 (1.0-3.0)	2.0 (1.0-3.0)	3.0 (2.0-5.0)	< 0.001
Clinical outcomes at data cutoff, *n* (%)				
Hospital discharge	210 (47.8)	68 (48.9)	142 (47.3)	0.757
Death	123 (28.0)	24 (17.3)	99 (33.3)	< 0.001
Still hospitalization	78 (17.8)	36 (25.9)	42 (14.0)	0.002
Transferred to another hospital	28 (6.4)	11 (7.9)	17 (5.7)	0.370

[1]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
[2]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range; GCS: Glasgow coma scale; NRS: Nutrition risk screening; GI: Gastrointestinal; ICU: Intensive care unit.

P = 0.310) and more complications, including disseminated intravascular coagulation (27.8% *vs* 54.2%, P = 0.007) and acute respiratory distress syndrome (12.0% *vs* 54.2%, P < 0.001). They also showed higher recovery rates than did those who had symptoms for more than 4 d (56.3% *vs* 27.8%, P = 0.004).

DISCUSSION

In this retrospective, multi-center study, we reported the incidence of GI manifestations among critically ill adult patients with heatstroke admitted to ICUs in the Sichuan Province, China. Our data demonstrated that patients with GI symptoms had a significantly longer ICU stay compared with those without. As a manifestation of systemic organ damage in heatstroke, the appearance of GI symptoms affect patients' EN therapy outcomes. Patients with older age and a lower GCS score on admission were more likely to experience GI symptoms. Our study provides valuable real-world evidence regarding the associations between heatstroke and GI symptoms with, to our knowledge, the highest number of patients from multiple centres to date.

Conventionally, critically ill patients with have GI dysfunction; however, there is little evidence supporting this phenomenon among heatstroke patients. Due to the lack of standardization of the diagnostic and therapeutic approaches, in this study, we evaluated the GI tract according to its symptoms and found that 18.5% of patients with heatstroke suffered from said symptoms during their stay. Compared with other non-heat stroke critically ill patients, the incidence of GI symptoms in our cohort is relatively low[9,10]. This is partly due to the fact that our study only used symptoms to evaluate GI function, though other high-incidence studies generally included physical examination, including that for bowel sounds, for comprehensive evaluation. When comparing the same symptoms, such as vomiting, between patients with heatstroke and those in the ICU, we observed that the incidence of GI symptoms in heatstroke patients is still lower than that of patients in the general ICU. One reason behind this is that heatstroke patients do not have GI structural damage from the perspective of pathogenesis, but patients in the general ICU comprise those who underwent abdominal surgery, that is, those who already have GI structural disorders. Another reason is that our study only assessed GI symptoms without other indicators such as physical examination, which may have led to the underestimation of the incidence of GI dysfunction. Nevertheless, our research suggests that GI injury is an important high-incidence manifestation of organ failure among heatstroke patients.

Our study found that heatstroke patients with older age and lower GCS score were more likely to experience GI symptoms. Multiple clinical studies had described risk factors for GI dysfunction in critically ill patients, including older age, larger BMI, lower Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores, surgical laparotomy, and use of mechanical ventilation, analgesic sedation, and vasopressors[9-11]. Similar to other studies, our study also observed that older patients were more likely to experience GI symptoms after heatstroke. Of note, our study found that the degree of nervous system damage, as quantified by the GCS score, is also related to the occurrence of GI dysfunction. This may be because heat damages the enteric nervous system, as well as the central nervous system. Moreover, patients with lower GCS scores were more likely to receive mechanical ventilation and vasopressors, posing an impact on the intestinal blood supply and, consequently, possibly leading to GI failure. The causes of GI dysfunction caused by heatstroke warrant further research.

We also observed that the presence of GI symptoms may affect EN support therapy. In our study, we found heatstroke patients who did not receive EN therapy within 48 h after ICU admission experienced more GI symptoms with more complications, longer ICU stay, and higher ICU mortality. The emergence of GI symptoms is the reason why EN cannot be started. Simultaneously, the failure to start EN support is also a reason for the deterioration of GI function. We also observed that a considerable proportion of patients with heat stroke still cannot implement total EN within 2 wk, suggesting that, for patients with heatstroke, further research to develop individualized nutrition support strategies is warranted.

We also performed various subgroup analyses to discuss different GI symptoms and whether their timing and duration had an impact on patient prognosis. First, we found that patients with different GI symptoms have different clinical features. Different symptoms may indicate that the severity of heatstroke in these patients varies, and whether this reflects their prognosis to some extent requires further study. The onset of GI symptoms in patients also differed. Overall, the earlier the GI symptoms appeared, the severer the patient's condition was. At the same time, due to GI symptoms, such patients could not tolerate EN or could not meet EN standards, further impairing their GI function and forming a vicious circle. Better approaches for EN support in these patients are warranted. Finally, we discussed the duration of the patient's GI symptoms. This was the same as we previously realized: The longer the duration of GI symptoms, the worse their prognosis. These patients were unable to start EN therapy early on. In contrast, they were more likely to have GI microcirculation disorders and damage to the intestinal barrier.

Currently, the cause of GI dysfunction caused by heatstroke is not particularly clear. Several reports have documented increased intestinal permeability during exercise with and without heat stress[4,12,13]. A murine model of classic heatstroke that induced a body core temperature as high as 42.7 °C showed considerable gut histological injury[14,15].

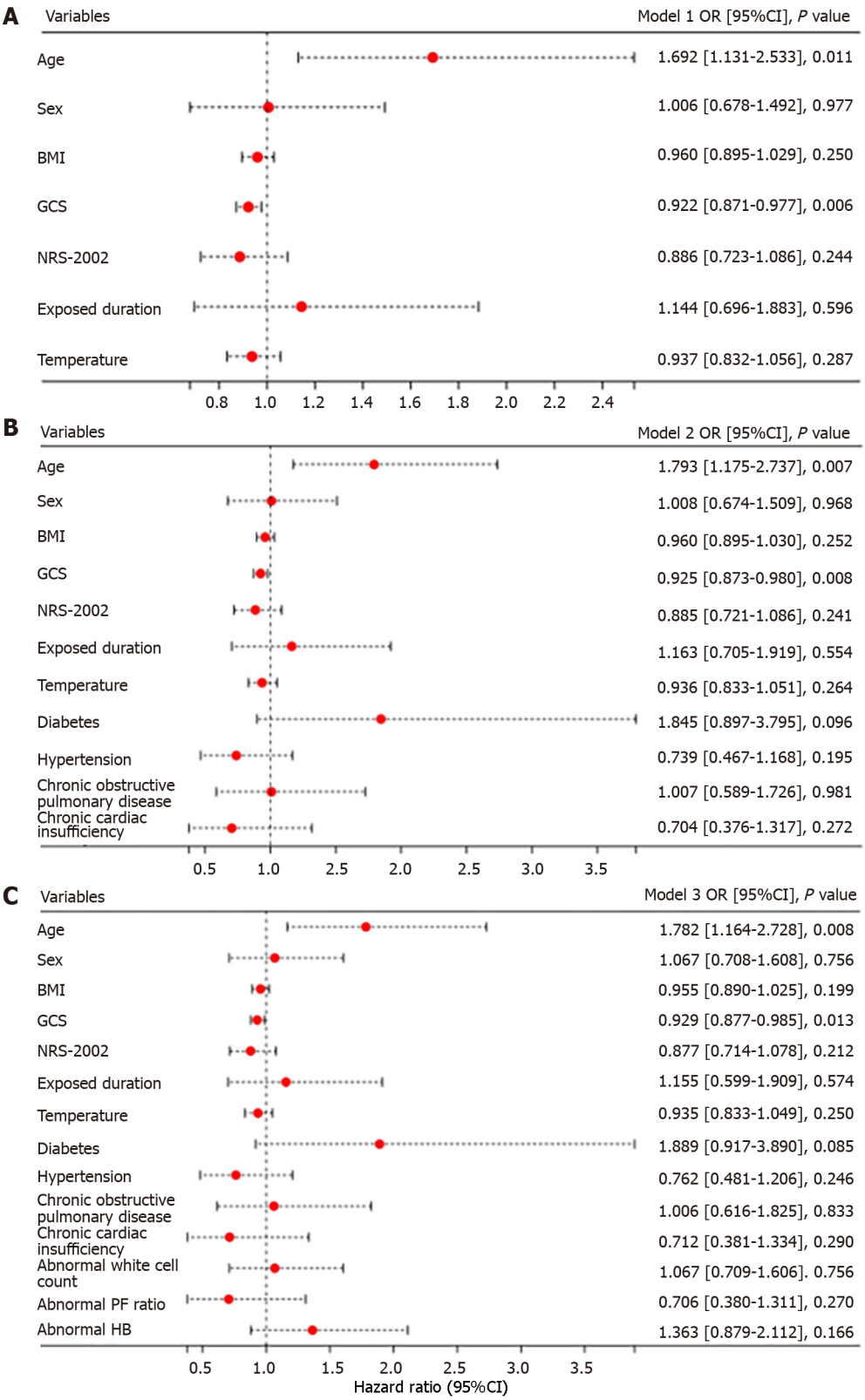

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Figure 3 Multivariable-adjusted logistic regression of risk factors with gastrointestinal symptoms. A: It showed multivariable logistic regression between heatstroke patients' gastrointestinal (GI) symptoms with age, sex, body mass index (BMI) Glasgow coma scale (GCS) score, nutrition risk screening 2002 (NRS-2002) score, high temperature exposed duration and patients' temperature; B: It is adjusted for coexisting disorder and index in Figure 3A; C: It is adjusted for laboratory results at intensive care unit admission and index in Figure 3A. Age is a categorical variable bounded by the median age of the patient, with less than the median age being compared. Sex is the categorical variable, with women being compared. BMI, GCS score, NRS-2002, exposed duration and temperature are continuous variables. Diabetes, hypertension, chronic obstructive disease, chronic cardiac insufficiency, abnormal white cell count, PaO_2/FiO_2 ratio and hemoglobin are categorical variable. BMI: Body mass index; GCS score: Glasgow coma scale score; NRS-2002 score: Nutrition risk screening-2002 score; OR: Odds ratio; PF ratio: PaO_2/FiO_2 ratio; HB: Hemoglobin.

Studies have shown that one of the important mechanisms of heatstroke is the excessive opening of intestinal tight junctions, destruction of intestinal cell structure and function, increase in intestinal mucosal permeability, and introduction of endotoxin into the blood[16,17]. One of the most frequently mentioned mechanisms of how heatstroke causes GI symptoms is the leaky gut hypothesis. Our results also suggest that while heat can cause changes in the state of consciousness caused by central nervous system damage, it may also cause damage to the enteric nervous system, thereby causing GI dysfunction. Such inferences need further research to confirm in the future.

The retrospective design of this study offers several benefits, including a high quality of data and a large number of patients. Our study provides a real-world representation of the current clinical practices for heatstroke in a mixed population of critically ill adult patients treated in ICUs in Sichuan Province, China. The patient sample size provides a robust representation of the target population, increasing the generalizability of our findings. Overall, our study provides important insights into the prevalence of GI symptoms among critically ill heatstroke patients and its relationship with risk factors and clinical outcomes. The findings of this study have important implications for the management and care of critically ill patients with heatstroke. Previous literature has demonstrated the vulnerability of the digestive tract to abnormal conditions, including hypoxia and elevated temperatures[4,12,13,18,19]. Studies have also indicated that most patients experience some form of GI symptoms during intense physical activity and elevated body temperature[20]. Our study on GI symptoms following heatstroke incorporates risk factors and provides a comprehensive understanding of the subject, thereby supplementing previous research.

Nevertheless, this study had some limitations. First, the use of GI symptoms to respond to GI dysfunction is one-sided. Another limitation is the exclusion of the most critically ill patients who had already passed away and those admitted to general wards. While this selection criterion was a necessary aspect of the research program, it is possible that the inclusion of these patients would not have greatly impacted the overall prognosis, as previously discussed. Our study was an observation of symptoms and did not address possible effects of treatment on GI function. Additionally, there is a high rate of missed diagnoses due to a lack of awareness of heatstroke in remote mountainous areas and the inadequate identification of heatstroke in a timely manner.

CONCLUSION

The incidence of GI symptoms among heatstroke patients admitted to the ICU was reportedly 18.5% in our study. Patients who are older and with a lower GCS score on admission have an increased likelihood of developing GI symptoms. Heatstroke patients with GI symptoms found it more difficult to tolerate EN therapy than did those without. Patients with GI symptoms were found to have a higher incidence of complications. The earlier the GI symptoms appeared and the longer the duration of GI symptoms, the more difficult it was for patients to tolerate EN, and the worse the predicted prognosis.

Table 4 Characteristics of the heatstroke patients with endotracheal intubation, according to received full enteral nutrition after intensive care unit admission or not[1]

	All intubated patients (*n* = 439)	Full EN whether		*P* value
		Yes (*n* = 173)	No (*n* = 266)	
Characteristic				
Age, median (IQR), yr	71.0 (63.0-80.0)	72.0 (63.0-80.0)	71.0 (63.0-79.0)	0.801
Female sex, *n* (%)	197 (44.9)	81 (46.8)	116 (43.6)	0.509
GCS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	6.0 (4.0-8.0)	5.0 (3.0-7.0)	0.002
NRS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	4.5 (4.0-5.0)	4.0 (3.0-5.0)	0.193
Body temperature on admission				
Patients, *n* (%)	439 (100.0)	173 (100.0)	266 (100.0)	–
Temperature, median (IQR), °C	41.0 (40.0-41.8)	41.0 (40.0-41.4)	41.0 (40.0-42.0)	0.128
Laboratory findings, median (IQR)				
PaO_2/FiO_2 ratio	225.0 (135.5-306.5)	246.0 (191.0-334.0)	222.0 (134.0-315.0)	0.226
White-cell count, 10^9/L	11.7 (8.1-15.6)	12.6 (9.4-16.7)	11.4 (8.0-15.3)	0.287
Lymphocyte count, 10^9/L	1.7 (0.8-2.8)	0.8 (0.5-1.6)	2.0 (0.9-3.0)	0.084
Platelet count, 10^9/L	92.0 (56.0-138.0)	71.5 (37.0-113.8)	89.0 (54.0-132.5)	0.011
Hemoglobin, g/L	124.0 (109.0-139.0)	119.0 (107.5-129.0)	125.0 (110.0-140.0)	0.002

Albumin, g/L	35.3 (32.5-38.9)	32.0 (29.0-35.2)	35.5 (32.5-39.2)	< 0.001
GI symptoms[2], *n* (%)				
Total patients	85 (19.4)	25 (14.5)	60 (22.6)	0.036
Diarrhea	60 (13.7)	17 (9.8)	43 (16.2)	0.059
Flatulence	25 (5.7)	8 (4.6)	17 (6.4)	0.435
Nausea/vomiting	14 (3.2)	7 (4.0)	7 (2.6)	0.409
Bloody stools	8 (1.8)	0 (0.0)	8 (3.1)	0.021
Complications, *n* (%)				
Disturbance of water and electrolyte	271 (61.7)	105 (60.7)	166 (62.4)	0.718
Rhabdomyolysis	81 (18.5)	20 (11.6)	55 (20.7)	0.013
Myocardial damage	216 (49.2)	83 (48.0)	133 (50.0)	0.678
Disseminated intravascular coagulation	172 (39.2)	60 (34.7)	112 (42.1)	0.119
Acute respiratory distress syndrome	226 (51.5)	92 (53.2)	134 (50.4)	0.566
Acute kidney injury	233 (53.1)	79 (45.7)	154 (57.9)	0.012
Acute liver function impairment	332 (75.6)	94 (54.3)	138 (51.9)	0.615
Central nervous system damage	206 (46.9)	80 (46.2)	126 (47.4)	0.817
Treatments				
Use of continuous renal-replacement therapy, *n* (%)	34 (7.7)	14 (8.1)	20 (7.5)	0.826
Length of ICU stay, median (IQR), d	2.0 (1.0-3.0)	2.0 (1.0-2.0)	3.0 (1.0-4.0)	< 0.001
Clinical outcomes at data cutoff, *n* (%)				
Hospital discharge	210 (47.8)	83 (48.0)	127 (47.7)	0.962
Death	123 (28.0)	29 (16.8)	94 (35.3)	< 0.001
Still hospitalization	78 (17.8)	46 (26.6)	82 (20.8)	0.339
Transferred to another hospital	28 (6.4)	15 (8.7)	13 (4.9)	0.113

[1]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
[2]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range; GCS: Glasgow coma scale; NRS: Nutrition risk screening; GI: Gastrointestinal; ICU: Intensive care unit.

Table 5 Clinical characteristics of the study patients, according to types of gastrointestinal symptoms[1]

	GI Symptoms[2]			*P* value
	Diarrhea (*n* = 88)	Flatulence (*n* = 27)	Nausea/vomiting (*n* = 15)	
Characteristic				
Age, median (IQR), yr	65.0 (56.0-76.0)	69.0 (56.0-79.0)	68.0 (57.5-78.0)	0.565
Female sex, *n* (%)	35.0 (39.8)	14.0 (51.8)	6 (40.0)	0.529
GCS score at ICU admission, median (IQR)	5.0 (3.0-7.0)	6.0 (3.0-9.5)	4.0 (3.0-6.0)	0.540
NRS score at ICU admission, median (IQR)	4.0 (3.0-5.0)	4.5 (4.0-5.0)	4.0 (3.0-5.0)	0.193
Body temperature admission				
Patients, *n* (%)	88.0 (100.0)	27.0 (100.0)	15.0 (100.0)	–
Temperature, median (IQR), °C	41.0 (40.0-42.0)	40.0 (39.8-41.0)	40.1 (39.8-41.0)	0.003
Complaints and symptoms, *n* (%)				
Fever	62.0 (70.5)	20.0 (74.0)	8.0 (53.3)	0.343

Altered mental state or behavior	35.0 (39.8)	13.0 (48.1)	4.0 (26.7)	0.395
Dry skin or excessive sweating	19.0 (21.6)	2.0 (7.4)	2.0 (13.3)	0.215
Rubefaction	7.0 (8.0)	2.0 (7.4)	1.0 (6.7)	0.983
Fast pulse	32.0 (36.4)	6.0 (22.2)	4.0 (26.7)	0.344
Polypnea	29.0 (33.0)	6.0 (22.2)	3.0 (20.0)	0.397
Headache	1.0 (1.1)	3.0 (11.1)	0.0 (0.0)	0.024
Syncope	63.0 (71.6)	13.0 (48.1)	8.0 (53.3)	0.052
Other	22.0 (25.0)	4.0 (14.8)	2.0 (13.3)	0.378
Laboratory findings, median (IQR)				
White-cell count, 10^9/L	13.0 (8.2-16.3)	13.0 (8.2-16.3)	13.0 (8.2-16.3)	0.210
Hemoglobin, g/L	122.0 (110.3-136.0)	125.0 (110.5-137.5)	120.0 (107.3-130.0)	0.589
Albumin, g/L	35.8 (32.9-38.8)	35.3 (32.0-39.5)	36.7 (29.3-39.5)	0.969
Complications, *n* (%)				
Disturbance of water and electrolyte	63 (71.6)	20 (74.0)	11 (73.3)	0.085
Rhabdomyolysis	24 (27.3)	6 (22.2)	4 (26.7)	0.003
Myocardial damage	49 (55.7)	11.0 (40.7)	9 (60.0)	0.008
Disseminated intravascular coagulation	40 (45.5)	9 (33.3)	6 (40.0)	0.010
Acute respiratory distress syndrome	46 (52.3)	9 (33.3)	6 (40.0)	0.012
Acute kidney injury	52 (59.1)	15 (55.6)	10 (66.7)	0.024
Acute liver function impairment	52 (59.1)	15 (55.6)	10 (66.7)	0.024
Central nervous system damage	48 (54.5)	15 (55.6)	9 (60.0)	0.019
Treatments				
Use of continuous renal-replacement therapy, *n* (%)	7 (8.0)	3 (11.1)	2 (13.3)	< 0.001
Length of ICU stay, median (IQR), d	1.0 (1.0-2.0)	1.0 (1.0-1.0)	2.0 (1.0-3.0)	0.015
Clinical outcomes at data cutoff, *n* (%)				
Hospital discharge	44.0 (50.0)	11.0 (40.7)	5.0 (33.3)	0.400
Death	16.0 (18.2)	2.0 (7.4)	4.0 (26.7)	0.240
Still hospitalization	19.0 (21.6)	13.0 (48.1)	5.0 (33.3)	0.025
Transferred to another hospital	9.0 (10.2)	1.0 (3.7)	1.0 (6.7)	0.547

[1]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
[2]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range; GCS: Glasgow coma scale; NRS: Nutrition risk screening; GI: Gastrointestinal; ICU: Intensive care unit.

Table 6 Heat stroke patient characteristics according to the time of onset of gastrointestinal symptoms

	GI symptoms[1]		*P* value
	On admission (*n* = 68)	Developed in ICU stay (*n* = 64)	
Characteristic			
Age, median (IQR), yr	67.0 (57.0-76.0)	70.0 (64.0-80.0)	0.050
Female sex, *n* (%)	28 (41.2)	32 (50.0)	0.310
BMI, median (IQR), kg/m^2	22.7 (20.2-24.8)	21.1 (20.0-23.3)	0.050
GCS score at ICU admission, median (IQR)	5.0 (3.0-8.0)	5.0 (3.0-7.0)	0.814

NRS score at ICU admission, median (IQR)	3.0 (3.0-4.5)	4.0 (3.0-6.0)	0.009
Fever on admission			
Patients, *n* (%)	68 (100.0)	64 (100.0)	–
Temperature, median (IQR), °C	41.0 (40.0-42.0)	41.0 (40.0-41.3)	0.265
Complaints and symptoms on admission, *n* (%)			
Fever	54 (79.4)	39 (60.9)	0.020
Altered mental state or behavior	25 (36.8)	30 (46.9)	0.239
Dry skin or excessive sweating	13 (19.1)	7 (10^9)	0.190
Rubefaction	5 (7.4)	6 (9.4)	0.674
Fast pulse	27 (39.7)	13 (20.3)	0.015
Polypnea	24 (35.3)	14 (21.9)	0.089
Headache	1 (1.5)	2 (3.1)	0.524
Syncope	49 (72.1)	36 (56.2)	0.058
Other	20 (29.4)	7 (10^9)	0.009
Coexisting disorder, *n* (%)			
Diabetes	1 (1.5)	9 (14.1)	0.009
Hypertension	15 (22.1)	21 (32.8)	0.166
Chronic obstructive pulmonary disease	11 (16.2)	10 (15.6)	0.931
Chronic cardiac insufficiency	5 (7.4)	11 (17.2)	0.084
Hepatitis B infection	1 (1.5)	0 (0.0)	0.330
Cancer	1 (1.5)	2 (3.1)	0.524
Chronic renal disease	0 (0.0)	2 (3.1)	0.142
Immunodeficiency	1 (1.5)	2 (3.1)	0.524
Laboratory findings			
PaO_2/FiO_2 ratio	240.0 (141.8-316.0)	217.0 (165.0-285.8)	0.775
White-cell count, 10^9/L	12.1 (7.8-16.2)	11.8 (8.2-14.2)	0.667
Lymphocyte count, 10^9/L	2.1 (1.0-3.3)	1.2 (0.6-2.0)	0.023
Platelet count, 10^9/L	90.0 (60.5-120.3)	98.5 (67.8-150.5)	0.256
Hemoglobin, g/L	126.0 (112.0-135.5)	118.5 (103.5-137.5)	0.106
Albumin, g/L	36.5 (33.3-40.0)	35.0 (32.1-38.6)	0.093
Other findings, median (IQR)			
C-reactive protein, mg/L	5.0 (0.5-10.0)	5.0 (1.0-14.9)	0.605
Procalcitonin, ng/mL	1.4 (0.4-8.2)	9.3 (2.2-29.3)	0.055
Lactate dehydrogenase, U/L	465.0 (314.3-810.3)	382.5 (282.8-537.8)	0.263
Aspartate aminotransferase, U/L	123.9 (58.3-272.3)	107.2 (44.0-268.3)	0.152
Alanine aminotransferase, U/L	46.5 (26.2-112.4)	48.0 (27.1-89.5)	0.247
Total bilirubin, μmol/L	18.5 (12.8-25.9)	15.6 (10.1-23.0)	0.211
CK-Mb, U/L	10.1 (2.9-33.1)	8.7 (3.3-41.0)	0.214
Creatinine, μmol/L	131.1 (105.3-182.8)	137.0 (97.5-171.0)	0.628
D-dimer, mg/L	3.9 (2.5-11.5)	4.6 (1.9-12.7)	0.524
Minerals, median (IQR), mmol/L			
Sodium	132.0 (129.0-137.0)	133.9 (128.5-136.8)	0.959
Potassium	3.3 (3.0-3.9)	3.5 (2.9-3.8)	0.849

Lactate	4.2 (3.1-5.5)	3.6 (2.4-5.3)	0.649
Complication, *n* (%)			
Disturbance of water and electrolyte	51 (75.0)	44 (68.8)	0.424
Rhabdomyolysis	21 (30.9)	13 (20.3)	0.165
Myocardial damage	40 (58.8)	30 (46.9)	0.122
Disseminated intravascular coagulation	38 (55.9)	24 (37.5)	0.034
Acute respiratory distress syndrome	39 (57.4)	27 (42.2)	0.082
Acute kidney injury	45 (66.2)	38 (59.4)	0.419
Acute liver function impairment	41 (60.3)	40 (62.5)	0.795
Central nervous system damage	42 (61.8)	30 (46.9)	0.086
Clinical outcomes at data cutoff, *n* (%)			
Hospital discharge	35 (51.5)	29 (45.3)	0.479
Death	17 (25.0)	9 (14.1)	0.114
Still hospitalization	13 (19.1)	20 (31.3)	0.108
Transferred to another hospital	3 (4.4)	6 (9.4)	0.258

[1]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range; CK-Mb: Creatine kinase; GI: Gastrointestinal; ICU: Intensive care unit; BMI: Body mass index.

Table 7 Heat stroke patient characteristics according to the time of onset of gastrointestinal symptoms[1]

	Early onset, *n* = 41	Late onset, *n* = 23	*P* value
Characteristic[2]			
Age, median (IQR), yr	69.0 (62.3-79.0)	64.0 (56.0-76.0)	0.856
Female sex, *n* (%)	23 (56.1)	8 (34.8)	0.102
Fever on admission			
Patients, *n* (%)	41 (100.0)	23 (100.0)	–
Temperature, median (IQR), °C	41.0 (40.0-42.0)	40.7 (39.6-41.3)	0.338
Body temperature on admission, *n* (%)			
Fever	23 (56.1)	15 (65.2)	0.475
Altered mental state or behavior	19 (46.3)	11 (47.8)	0.909
Dry skin or excessive sweating	4 (9.8)	3 (13.0)	0.686
Rubefaction	4 (9.8)	2 (8.7)	0.889
Fast pulse	11 (26.8)	2 (8.7)	0.084
Polypnea	9 (22.0)	5 (21.7)	0.984
Headache	2 (4.9)	0 (0.0)	0.282
Syncope	21 (51.2)	13 (56.5)	0.683
Other	3 (7.3)	4 (17.4)	0.215
EN support			
EN, *n* (%)	29 (70.7)	22 (95.7)	< 0.001
Average EN calorie, median (IQR), kcal/d	752.0 (500.0-1007.5)	1292.0 (750.0-1560.0)	< 0.001
Average EN protein, median (IQR), g/d	20.0 (17.6-32.5)	28.0 (15.0-57.0)	0.003
Average EN volume, median (IQR), ml/d	600.0 (147.5-1000.0)	900.0 (461.2-1500.0)	< 0.001
Duration of EN, median (IQR), d	3.0 (1.8-5.0)	7.0 (4.0-11.0)	0.011

Laboratory findings, median (IQR)			
White-cell count, 10^9/L	10.6 (7.8-13.5)	13.5 (8.6-15.8)	0.351
Hemoglobin, g/L	117.0 (106.0-128.0)	128.5 (105.3-141.5)	0.187
Albumin, g/L	35.4 (33.7-39.2)	34.4 (30.8-36.8)	0.239
Complications, *n* (%)			
Disturbance of water and electrolyte	26 (63.4)	17 (73.9)	0.391
Rhabdomyolysis	6 (14.6)	6 (26.1)	0.261
Hemorrhage of digestive tract	8 (19.5)	3 (13.1)	0.511
Myocardial damage	17 (41.5)	12 (52.2)	0.409
Disseminated intravascular coagulation	14 (34.1)	9 (39.1)	0.691
Acute respiratory distress syndrome	17 (41.5)	6 (26.1)	0.855
Clinical outcomes at data cutoff, *n* (%)			
Hospital discharge	17 (41.5)	11 (47.8)	0.622
Death	7 (17.1)	2 (8.7)	0.355
Still hospitalization	12 (29.3)	8 (34.8)	0.648
Transferred to another hospital	4 (9.8)	2 (8.7)	0.889

[1]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
[2]The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding.
IQR: Interquartile range; EN: Enteral nutrition.

Table 8 Heat stroke patient characteristics according to duration of gastrointestinal symptoms[1]

	Last < 4 d, *n* = 96	Last ≥ 4 d, *n* = 36	*P* value
Characteristic			
Age, median (IQR), yr	70.0 (61.5-78.3)	67.0 (59.0-76.0)	0.659
Female sex, *n* (%)	43 (44.8)	17 (47.2)	0.803
Body temperature on admission			
Patients, *n* (%)	96 (100.0)	36 (100.0)	-
Temperature, median (IQR), °C	41.0 (40.0-41.5)	41.0 (40.0-42.0)	0.948
Complaints and symptoms on admission, *n* (%)			
Fever	69 (71.9)	24 (66.7)	0.559
Altered mental state or behavior	39 (40.6)	16 (44.4)	0.692
Dry skin or excessive sweating	16 (16.7)	4 (11.1)	0.428
Rubefaction	9 (9.4)	2 (5.6)	0.889
Fast pulse	32 (33.3)	8 (22.2)	0.767
Polypnea	31 (32.3)	7 (19.4)	0.147
Headache	2 (2.1)	1 (2.8)	0.811
Syncope	67 (69.8)	18 (50.0)	0.034
Other	19 (19.8)	8 (22.2)	0.758
Laboratory findings, median (IQR)			
White-cell count, 10^9/L	11.0 (7.5-14.2)	7.3 (9.2-16.3)	0.062
Hemoglobin, g/L	122.0 (110.5-135.5)	118.0 (106.0-132.5)	0.941
Albumin, g/L	37.0 (33.3-39.7)	34.4 (31.1-36.4)	0.031

Complications, *n* (%)			
Disturbance of water and electrolyte	69 (71.9)	20 (55.6)	0.075
Rhabdomyolysis	28 (29.2)	6 (16.7)	0.144
Hemorrhage of digestive tract	28 (29.2)	7 (19.4)	0.26
Myocardial damage	50 (52.1)	20 (55.6)	0.722
Disseminated intravascular coagulation	27 (27.8)	20 (54.2)	0.007
Acute respiratory distress syndrome	12 (12.0)	20 (54.2)	< 0.001
Clinical outcomes at data cutoff, *n* (%)			
Hospital discharge	54 (56.3)	10 (27.8)	0.004
Death	17 (17.7)	9 (25.0)	0.348
Still hospitalization	21 (21.9)	12 (33.3)	0.176
Transferred to another hospital	4 (4.2)	5 (13.9)	0.048

[1]Nausea/vomiting, diarrhea, flatulence, or bloody stools are defined as gastrointestinal symptoms.
IQR: Interquartile range.

ARTICLE HIGHLIGHTS

Research background
Extreme heat exposure is a growing health problem. The effects of heat on the gastrointestinal tract is unknown.

Research motivation
It was intended to summarize the effects of heat on the gastrointestinal (GI) tract of intensive care unit (ICU) patients.

Research objectives
This study aimed to assess the incidence of GI symptoms associated with heatstroke and its impact on outcomes.

Research methods
We conducted a retrospective, multi-center, observational cohort study to analyze outcomes between patients.

Research results
The timing and duration of gastrointestinal symptoms affects heatstroke patient's prognosis and enteral nutrition (EN) therapy. The status of EN therapy is related to heatstroke patients' outcomes. Advanced age and low Glasgow coma scale (GCS) scores are risk factors for gastrointestinal symptoms in heatstroke patients.

Research conclusions
The GI manifestations of heatstroke are common and appear to impact clinically relevant hospitalization outcomes.

Research perspectives
This was a retrospective, multi-center, observational cohort study that involved patients admitted to 83 ICUs located in 16 cities in the Sichuan Province, China between June 1 and October 31, 2022. Results showed older heatstroke patients with a lower GCS score on admission were more likely to experience GI symptoms, which had statistical difference. Clinicians should pay attention to the time at which heatstroke patients started manifesting gastrointestinal symptoms, as well as the duration of said symptoms, to ensure that patients are timely treated with the proper EN therapy and have the best prognosis possible.

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FOOTNOTES

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