88624_Auto_Edited.docx

WORD COUNT	5470	TIME SUBMITTED	18-DEC-2023 01:01PM
		PAPER ID	105567345

Name of Journal: *World Journal of Gastroenterology*
Manuscript NO: 88624
Manuscript Type: ORIGINAL ARTICLE

Observational Study

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

Gastrointestinal manifestations of critical-ill heatstroke patients

Yu-cong Wang, Xin-yang Jin, Zheng Lei, Xiao-jiao Liu, Yu Liu, Bang-guo Zhang, Jian Gong, Lie-tao Wang, Lv-yuan Shi, Ding-yuan Wan, Xin Fu, Lu-ping Wang, Ai-jia Ma, Yi-song Cheng, Jing Yang, Min He, Xiao-dong Jin, Yan Kang, Bo Wang, Zhong-wei Zhang, Qin Wu

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

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.

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

Wang YC, Jin XY, Lei Z, Liu XJ, Liu Y, Zhang BG, Gong J, Wang LT, Shi LY, Wan DY, Fu X, Wang LP, Ma AJ, Cheng YS, Yang J, He M, Jin XD, Kang Y, Wang B, Zhang ZW, Wu Q. Gastrointestinal manifestations of critical ill heatstroke patients and their associations with outcomes: A multicentre, retrospective, observational study. *World J Gastroenterol* 2023; In press

Core Tip: This study aimed to assess the incidence of gastrointestinal symptoms associated with heatstroke and its impact on outcomes. This was a retrospective, multi-center, observational cohort study that involved patients admitted to 83 ICUs (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 GCS (Glasgow Coma Score) score on admission were more likely to experience GI (gastrointestinal) 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 (enteral) therapy and have the best prognosis possible.

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 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 gastrointestinal 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 ICU in 2022. Our study primarily aimed to determine the incidence of gastrointestinal disturbances among patients experiencing heatstroke from various medical centres in the Sichuan Province, with a secondary objective of identifying the risk factors for gastrointestinal 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 number: 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 (YCW, LTW, LYS, and DYW) reviewed all data independently for completeness and accuracy, and the data management team (MH, JY

and QW) conducted a thorough cleaning of the data, identifying any missing information.

Data comprising baseline information, laboratory test results, treatment plan, gastrointestinal symptoms, nutrition support, and patient outcome were collected in the electronic data capture system. As demographic information, age, gender, 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 days, it was defined as a high temperature heat wave. Treatment received during the observation period, including organ support technical, antibiotics, and steroids, were recorded.

Gastrointestinal 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 days, 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 procyne 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 ECG (electrocardiogram). Acute kidney injury was defined according to the KDIGO (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.

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, USA). 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$\chi 2$ 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, USA).

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 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 gastrointestinal 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, as shown in 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, aP=0.018) and lower NRS-2002 scores (3.0 vs. 4.0, bP=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%,

cP=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, dP=0.014) and hemoglobin (115.0 vs. 124.0, eP=0.014) and a higher level of blood lactate (3.1 vs. 3.4, eP=0.036) and C-reactive protein (11.9 vs. 5.0, fP=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%, gP=0.003), acute liver function impairment (61.4%, hP <0.001), and central nervous system damage (56.1%, iP=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 gastrointestinal symptoms (jP=0.001, Figure 3a). Moreover, patients with a lower GCS score were prone to have GI symptoms (kP=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 gastrointestinal 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 gastrointestinal 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, lP=0.002), experienced more gastrointestinal symptoms after ICU admission (22.3% vs. 12.9%, mP=0.021), and had a longer ICU stay

(3.0 vs. 2.0, nP <0.001). Logistic regression analysis showed that gastrointestinal symptoms were an independent risk factor for not initiating early enteral nutrition (oP=0.037, Supplementary Figure 3). During the observational period, 266 (60.6%) patients with endotracheal intubation at admission failed to establish full EN (Table 4). Patients who do not receive full EN experienced more GI symptoms (22.6% vs. 14.5%, pP=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%, qP<0.001). Moreover, rhabdomyolysis (20.7% vs. 11.6%, rP=0.013) and acute kidney injury (57.9% vs. 45.7%, sP=0.012) were more common, and ICU stay was longer in the former population (3.0 vs. 2.0, tP<0.001).

Subgroup analysis

Since the definition of gastrointestinal 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 gastrointestinal manifestations (Table 5). There was a statistically significant difference in temperature on admission between patients with diarrhoea, flatulence, and nausea/vomiting (uP=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 (vP=0.025).

As we observed that the onset of gastrointestinal symptoms was significantly different between patients, we further divided patients with gastrointestinal symptoms into two categories: those with gastrointestinal symptoms on ICU admission and those with gastrointestinal symptoms developed during ICU stay. The patient characteristics of both groups are shown in Table 6. The patients who had gastrointestinal symptoms on admission were younger (vP=0.050), had a higher body mass index (BMI) (22.7 vs. 21.1,

wP=0.050), and had a lower nutrition risk screening (NRS-2002) score on admission (3.0 vs. 4.0, xP=0.009) than had those who developed symptoms later on. Patients who had less gastrointestinal symptoms on admission had a lower number of comorbidities, including diabetes (1/68, 1.5% vs. 9/64, 14.1%, yP=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 days of ICU stay) and late-onset groups (≥3 days 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%, zP<0.001). The early-onset group received less EN calorie (752.0 kcal/ds [IQR: 500.0–1007.5] vs. 1292.0 kcal/ds [IQR: 750.0-1560.0]), protein (20.0 g/ds [IQR: 17.6–32.5] vs. 28.0 g/ds [IQR: 15.0–57.0]), and EN volume (600.0 mL/ds [IQR: 147.5–1000.0] vs. 900.0 mL/ds [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 ds [IQR: 1.8–5.0] vs. 7.0 ds [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 gastrointestinal symptoms for more than 4 days and those who did for had GI symptoms for less than 4 days, as shown in Table 8. Patients with gastrointestinal symptoms for at least 4 days had lower albumin levels (37.0 g/L vs, 34.4 g/L, 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 days (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 gastrointestinal symptoms affect patients' EN therapy outcomes. Patients with older age and a lower GCS score on admission were more likely to experience gastrointestinal symptoms. Our study provides valuable real-world evidence regarding the associations between heatstroke and gastrointestinal symptoms with, to our knowledge, the highest number of patients from multiple centres to date.

Conventionally, critically ill patients with have gastrointestinal 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 gastrointestinal 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 gastrointestinal symptoms in our cohort is relatively low[9, 10]. This is partly due to the fact that our study only used symptoms to evaluate gastrointestinal 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 gastrointestinal 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 gastrointestinal 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 gastrointestinal structural disorders. Another reason is that our study only assessed gastrointestinal symptoms without other indicators such as

physical examination, which may have led to the underestimation of the incidence of gastrointestinal dysfunction. Nevertheless, our research suggests that gastrointestinal 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 gastrointestinal symptoms. Multiple clinical studies had described risk factors for gastrointestinal dysfunction in critically ill patients, including older age, larger BMI, lower APACHE II and SOFA 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 gastrointestinal 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 gastrointestinal 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 gastrointestinal failure. The causes of gastrointestinal dysfunction caused by heatstroke warrant further research.

We also observed that the presence of gastrointestinal 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 gastrointestinal symptoms with more complications, longer ICU stay, and higher ICU mortality. The emergence of gastrointestinal symptoms is the reason why EN cannot be started. Simultaneously, the failure to start EN support is also a reason for the deterioration of gastrointestinal function. We also observed that a considerable proportion of patients with heat stroke still cannot implement total enteral nutrition 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 gastrointestinal symptoms and whether their timing and duration had an impact on patient prognosis. First, we found that patients with different gastrointestinal 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 gastrointestinal symptoms in patients also differed. Overall, the earlier the gastrointestinal symptoms appeared, the severer the patient's condition was. At the same time, due to gastrointestinal symptoms, such patients could not tolerate enteral nutrition or could not meet enteral nutrition standards, further impairing their gastrointestinal function and forming a vicious circle. Better approaches for enteral nutrition support in these patients are warranted. Finally, we discussed the duration of the patient's gastrointestinal symptoms. This was the same as we previously realized: The longer the duration of gastrointestinal symptoms, the worse their prognosis. These patients were unable to start EN therapy early on. In contrast, they were more likely to have gastrointestinal microcirculation disorders and damage to the intestinal barrier.

Currently, the cause of gastrointestinal 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]. 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 gastrointestinal 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 gastrointestinal 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 gastrointestinal 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 gastrointestinal symptoms during intense physical activity and elevated body temperature[20]. Our study on gastrointestinal 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 gastrointestinal symptoms to respond to gastrointestinal 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 gastrointestinal 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 gastrointestinal symptoms. Heatstroke patients with gastrointestinal symptoms found it more difficult to tolerate EN therapy than did those without. Patients with gastrointestinal symptoms were found to have a higher incidence of complications. The earlier the gastrointestinal symptoms appeared and the longer the duration of gastrointestinal symptoms, the more difficult it was for patients to tolerate EN, and the worse the predicted prognosis.

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 tract of 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 therapy. The status of enteral nutrition therapy is related to heatstroke patients' outcomes. Advanced age and low Glasgow Coma Scale 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.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all investigators who participated in this trial. A full list of members who participated in this study from the Heatstroke Research Group in Southwest China: Wei Tang (Dazhou Central Hospital), Yisong Ren (Chengdu Pidu District Traditional Chinese Medicine Hospital), Qionglan Dong (The Third People's Hospital of Mianyang), Maojuan Wang (Deyang People's Hospital), Lianghai Cao (Yibin Second People's Hospital), XianjunWang (The Second People's Hospital of Jiangyou City), Lang Tu (Shehong People's Hospital), Guanghong Ye (Anyue County

Hospital of Traditional Chinese Medicine), Li Chen (Guang'an District People's Hospital, Guang'an City), Anqin Li (The Fourth People's Hospital of Jiangyou City), Zhifu Liu (Jingyan County People's Hospital), Xiaolin Han (Pengzhou Traditional Chinese Medicine Hospital), Yu Dai (Mianyang Anzhou District People's Hospital), Xiong Yang (Langzhong People's Hospital), Jun Chen (Jianyang People's Hospital), Xianpeng Qiu (The Fourth People's Hospital of Zigong City), Senzhong Cheng (Zhongjiang County People's Hospital), Bo Qi (Sichuan Jiangyou 903 Hospital), Pan Yang (Meishan Cancer Hospital), Xuting Deng (Luxian People's Hospital), Qinya Ding (Linshui County Traditional Chinese Medicine Hospital), Chunmei Huang (Nanjiang County Traditional Chinese Medicine Hospital), Fangpei Zhang (Hejiang County Hospital of Traditional Chinese Medicine), Hongyu Yang (Mianyang Fulin Hospital), Xiaocui Wang (Deyang Hospital of Integrated Traditional Chinese and Medicine), Jiajin Li (Mianyang People's Hospital), Xiaojiao Liu (Guanghan People's Hospital), Xuemei Ye (Meishan People's Hospital), Fang Wu (Ziyang Lezhi County People's Hospital), Tao Ye (Leshan Traditional Chinese Medicine Hospital), Zhuo Tang (Zizhong County Traditional Chinese Medicine Hospital), Liang He (Pyeongchang County Traditional Chinese Medicine Hospital), Jiang Gong (Ziyang People's Hospital), Hongxu Chen (Leshan Traditional Chinese Medicine Hospital); Qionghua Hu, (Mianyang Central Hospital); Zhen Wang, (Shifang Second Hospital); Rong Hu, (Xingwen County People's Hospital); Youwei Li, (The Third People's Hospital of Anyue County); Lin Hou, (Bazhong Enyang District People's Hospital); Zhuo Chen, (The Third People's Hospital of Yibin); Huaqiang Shen, (Bazhong Central Hospital); Jian Wang, (Guang'an People's Hospital); Ping Fang, (Neijiang Second People's Hospital); Yu Liu, (Lezhi County Traditional Chinese Medicine Hospital in Sichuan Province); Yan Luo, (Luzhou Traditional Chinese Medicine Hospital); Weipeng Xu, (Fushun County People's Hospital); Chunlin Zhang, Yibin Traditional Chinese Medicine Hospital); Xiaoqi Tang, (Ziyang Yanjiang District People's Hospital); Yuliu, (Lezhi County People's Hospital); Jingmei Yang, (Qingshen County People's Hospital); Xinpin Yang, (Pyeongchang County People's Hospital, Bazhong City); Liang Chen, (Gaoxian People's Hospital);

Guangwei Yang, (Huaying People's Hospital); Chunhong Tang, (Jintang County First People's Hospital); Shihao Ren, (Zitong County People's Hospital); Jie Zhao, (Ziyang People's Hospital); Pin Li, (Shehong Hospital of Traditional Chinese Medicine); Ya Qiang, (Mianyang Traditional Chinese Medicine Hospital); Hongzhou Wang, (Sichuan Science City Hospital); Senzhong Cheng, (Sichuan Mianyang 404 Hospital); Songlin Wu, (Affiliated Hospital of Southwest Medical University); Lu Liu, (Luzhou Xuyong County People's Hospital); Xuecha Li, (Neijiang Dongxing District People's Hospital); Shihu Zhang, (Ya'an Yucheng District People's Hospital); He Lin, (Zizhong County People's Hospital); Xiaodong Feng, (Mianzhu People's Hospital); Jun Liang, Zitong County People's Hospital of Mianyang City (Zitong County People's Hospital of Mianyang City).

88624_Auto_Edited.docx

ORIGINALITY REPORT

2%
SIMILARITY INDEX

PRIMARY SOURCES

1	Gang Wang, Feng Min Luo, Dan Liu, Jia Shen Liu et al. "A Head-To-Head Comparative Study of Covid-19 Patients Between Epicenter and Peripheral Areas of Pandemic From China", Research Square, 2020 Crossref	48 words — 1%
2	www.ncbi.nlm.nih.gov Internet	37 words — 1%
3	Christian K Garcia, Liliana I Renteria, Gabriel Leite-Santos, Lisa R Leon, Orlando Laitano. "Exertional heat stroke: pathophysiology and risk factors", BMJ Medicine, 2022 Crossref	30 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 1%
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 10 WORDS