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# Heat Stroke as a Cause of Liver Failure and Evaluation of Liver Transplant

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## Abstract

Heat stroke is a multiple organ dysfunction syndrome of poorly understood pathogenesis. Exertional heat stroke with acute liver failure is a rarely reported condition. Liver transplant has been recommended as treatment in cases of severe liver dysfunction; however, there are only 5 described cases of long-term survival after this procedure in patients with heat stroke. Here, we present 2 cases of young athletes who developed heat stroke. Both patients developed acute liver failure and were listed for liver transplant. Liver function tests of one patient improved, and he was discharged on postoperative day 13. The other patient showed no signs of improvement and liver biopsy showed massive necrosis. The patient underwent combined kidney-liver transplant and was discharged on postoperative day 17. After a follow-up of longer than 6 years, both patients are doing well with normal liver function and no neurologic sequelae. We also reviewed all published cases of hepatic failure associated with heat stroke and found 9 published cases of liver transplant for heat stroke in the English literature. Conservative management appears to be justified in heat stroke-associated liver failure, even in the presence of accepted criteria for emergency liver transplant. If the liver does not show signs of recovery and hepatic decompensation progresses, liver transplant should be performed.

**Key words:** Acute liver failure, Emergency liver transplant, Elevated body temperature, Exertional heat stroke, Heat shock, Heat stroke-associated liver failure

## Introduction

Heat stroke (HS) is a multiple organ dysfunction syndrome of poorly understood pathogenesis. It is defined as having an elevated body temperature of more than 40°C with central nervous system dysfunction.<sup>1</sup> Heat stroke can be divided into 2 subtypes: classical or exertional. Classical HS is more common in elderly and immunocompromised individuals and is associated with elevated environmental temperatures. Exertional HS occurs in younger individuals and is associated with vigorous activities, such as long-distance running.<sup>1</sup> Potential complications after HS include acute renal failure, disseminated intravascular coagulation (DIC), rhabdomyolysis, acute respiratory distress syndrome, and hepatic failure, not uncommonly followed by death.<sup>2</sup> Although in the United States there have been an estimated 7233 heat-related deaths in a period of 10 years, few cases are directly related to HS.<sup>3</sup> It has been rarely reported that heat shock can lead to organ failure, and only a few case reports have described acute liver failure (ALF) due to HS.<sup>4-11</sup> Also, liver transplant has been recommended for treatment of severe liver failure; however, reports of long-term survival after this procedure in HS are scarce.

## Case Report

Patient 1 was a 28-year-old athletic man who collapsed after running 15 km. On initial presentation, he showed hyperthermia (40.6°C), ALF (Model for End Stage Liver Disease score of 40), kidney failure associated with rhabdomyolysis, DIC, and deterioration of cognitive function. Head computed tomography scan and toxicology panel results

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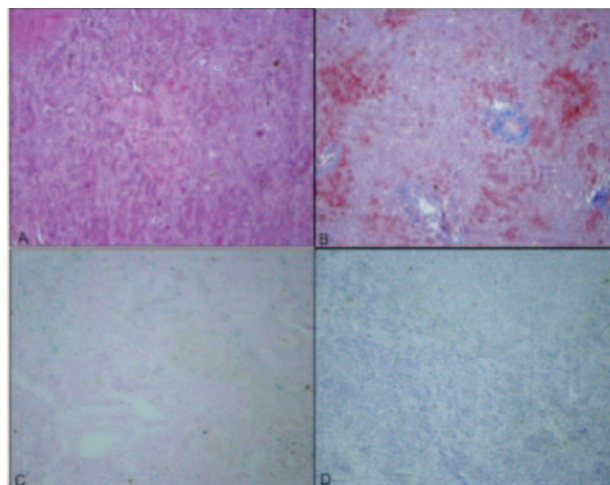
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were normal. Aspartate aminotransferase peaked at 12 010 IU/L and alanine aminotransferase at 9290 IU/L on day 2. Serum creatinine peaked at 7.1 mg/dL on day 2, creatinine kinase peaked at 110 000 U/L, total bilirubin peaked at 21.6 mg/dL on day 4, and international normalized ratio peaked at 3.7. The patient fulfilled the standard criteria for emergent liver transplant (United Network for Organ Sharing status 1A and King's College criteria) and was placed on the wait list. However, he was not transplanted because his liver function tests had improved several days after his clinical condition. Thirteen days after admission to the hospital, the patient was discharged with normal transaminase levels but residual cholestasis. Serum levels of liver enzymes and creatinine returned to normal 2 months after the liver injury, and the patient is currently doing well after more than 5 years.

Patient 2 was a 27-year-old patient, also an athlete and with no significant past medical history, who collapsed after running 2 km. He presented to the emergency room with hyperthermia (40.2°C), ALF (Model for End-Stage Liver Disease score of 42), kidney failure attributed to rhabdomyolysis, DIC, and change in mental status. Head computed tomography and magnetic resonance imaging, electroencephalogram, and toxicology panel results were all normal. Level of aspartate aminotransferase peaked at 26 610 IU/L and alanine aminotransferase at 20 510 IU/L on day 2. Creatinine was 7.5 mg/dL on day 2, creatinine kinase peaked at 100 000 U/L, international normalized ratio peaked at 11.9, and total bilirubin peaked at 47.1 mg/dL on day 16 and was 42.6 mg/dL at the time of transplant. The patient fulfilled the standard criteria for emergent liver transplant (United Network for Organ Sharing status 1 and King's College criteria), but we decided to observe for spontaneous clinical recovery. On day 20, there were no clinical signs of improvement, and liver and kidney biopsies were obtained. The liver biopsy showed massive necrosis (Figure 1), and the patient was listed for transplant. Electron microscopy did not show any signs of lysosomal storage disease or mitochondrial abnormalities. Kidney biopsies showed myoglobin cast nephropathy and severe acute tubular necrosis. Electron microscopy of the kidney showed severe effacement of foot processes of podocytes, suggestive of minimal change disease of focal segmental glomerulosclerosis. Muscle biopsy and electron microscopy did not reveal any muscular

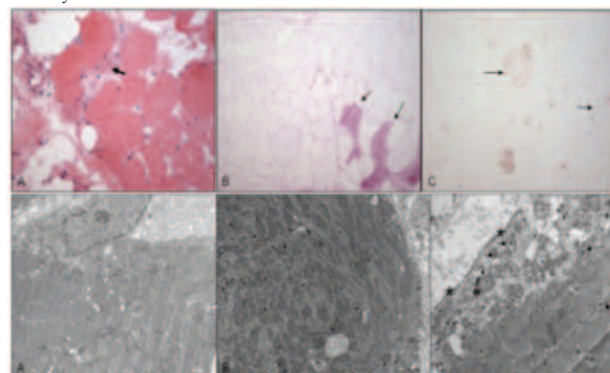
or mitochondrial pathology (Figure 2). On day 24 after admission, after conservative management had failed, the patient underwent combined liver and kidney transplant. Organs were derived from a 42-year-old standard criteria donor.

**Figure 1.** Liver Biopsy Performed on Day 20 After the Event Showing Panlobular Necrosis, Cholangitis, Ductular Proliferation, and Mild Fibrosis



(A) Hematoxylin and eosin staining. (B) Trypan blue staining. (C and D) Iron and copper staining were negative.

**Figure 2.** Muscle Biopsy Performed on Day 20 After the Event Ruled Out Primary Mitochondrial Disease



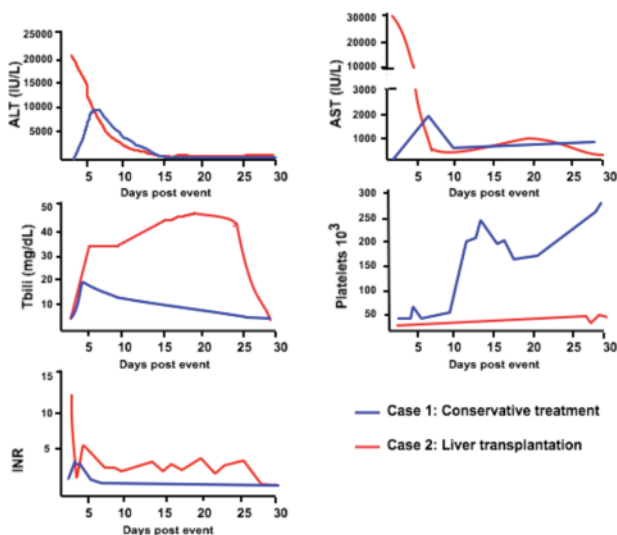
(A) Rare necrotic fibers. (B and C) Depletion of sarcoplasmic glycogen stores (only rare fibers with preserved stores indicated by arrows). The electron microscopy panels (bottom) show normal mitochondria below the sarcolemma.

The postoperative course was unremarkable; continuous venovenous hemodialysis was started on hospital day 2 and was stopped 3 days after transplant. The patient was discharged on postoperative day 17 to a rehabilitation facility with improving kidney function, normal mental status, and residual cholestasis. Liver function tests returned to normal 30 days after transplant.

Figure 3 shows liver function tests for both patients up to 30 days after the event. After follow-up

of more than 5 years, both patients have normal liver function and no neurologic sequelae.

Figure 3. Liver Function Tests After Heat Stroke



ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; Tbili, total bilirubin

## Discussion

We present 2 cases of previously healthy athletes (no preexisting liver disease) who collapsed during running and were hospitalized with altered mental status and a body temperature above 40°C. These constitute the early clinical features of exertional HS. Both cases of HS were complicated by ALF. The mechanisms leading to ALF and multiorgan failure are not yet fully understood. It is suggested that systemic inflammatory response leads to apoptosis and necrosis of hepatocytes.<sup>12</sup> Hepatic ischemia, due to microthrombosis and injury to the vascular endothelium, is thought to be implicated in the cause.<sup>13</sup> Liver injury in most cases of HS is usually asymptomatic and exhibits only mild reversible elevation in plasma aminotransferase levels. Prompt early recognition of HS and effective body cooling with attention to possible complications can result in complete recovery. However, in a minority of patients, the hepatic injury due to HS can result in death, which can occur 1 week or more after onset unless liver transplant is performed. A report from the Acute Liver Failure Study Group (including the participation of our center), which included 2675 consecutive patients enrolled in a prospective observational cohort between 1998 and 2015, showed 8 cases of HS with 5 patients meeting criteria for ALF.<sup>14</sup>

A PubMed search of the English literature (key words included liver, transplantation, and heat stroke) revealed 27 cases of HS-induced liver failure (Table 1). About 2/3 of these patients had spontaneous recovery, 1/3 of patients required transplant, and 1/4 died. There are only 9 previous cases of liver transplant for HS described in the literature. Of these 9 liver transplant recipients, 2 patients died within 1 year postoperatively. Currently, no guidelines are available for transplant after HS-induced liver failure. Davis and associates showed that, of 5 patients with HS-associated liver failure, 2 died within 48 hours of admission from multiorgan failure, 2 patients required vasopressors, 3 required intubation, and 1 required combined kidney and liver transplant (the same patient as in our series). No long-term sequelae were observed in survivors. They concluded that poor prognostic factors included temperature > 42°C, requirement of vasopressors, and rapid multiorgan failure.<sup>14</sup> In our analysis of the literature, there were only 4 cases with temperatures of > 42°C, but all of these patients survived (see Table 1).

Two cases of combined kidney and liver transplant have been described, and both were successful (see Table 1). Several patients with HS-induced liver failure have also had signs of renal failure and required renal replacement therapy.<sup>6-13</sup> Therefore, combined kidney and liver transplant may be considered for these patients. In our case, the critical status of the patient, a kidney biopsy showing severe tubular necrosis, and prolonged renal replacement therapy requirement supported this decision. Critically ill patients who require hemodialysis after liver transplant have increased mortality.<sup>15</sup> Living-donor liver transplant, which was successful in 2 patients in Asia, can also be life-saving in emergency situations.<sup>5,9</sup> However, the practice of using living donors in very sick patients is ethically controversial in Western countries.

Liver transplant is not always a life-saving treatment.<sup>10,11</sup> Berger and associates described continued renal failure and rhabdomyolysis after liver transplant, and twice-daily hemodialysis and respiratory support could not prevent death.<sup>10</sup> A comparable postoperative course was described by Saissy and colleagues, in which acute renal failure with severe rhabdomyolysis developed on day 4 posttransplant while the patient was perfectly alert. His condition thereafter deteriorated, and he died of

**Table 1.** Literature Search on All Published Cases of Liver Failure Associated With Heat Stroke

Reference	Activity Type	Max Temp, °C	Age, y	Liver Transplant	Survival	Peak AST, IU/L	Peak Bilirubin, mg/dL	Peak INR	Comments
Present study	15-km run	40.6	28	No	Yes (5- y follow-up)	12 010	21.6	3.7	
Present study	2-km run	39.2	27	Yes	Yes (5-y follow-up)	26 610	47.1	11.9	Combined kidney-liver transplant
Davis et al <sup>14</sup>	5 cases	40.6 to 42.2	25.5 to 35.5	1 patient	2/5 died; transplanted patient survived (1-y follow-up)	1784 to 9897	11 to 25.9	3.0 to 4.6	Combined kidney-liver transplant
Coenen et al <sup>4</sup>	Found in a dry air hot sauna	40.4	69	Yes	Yes (10-mo follow-up)	12 688	148	> 10	Needed intubation, renal replacement up to POD4
Inayat et al <sup>5</sup>	Found unresponsive inside a car	42.2	26	Yes (living donor)	Yes (1-y follow-up)	9129		9.1	Needed cryoprecipitate transfusion
Carvalho et al <sup>19</sup>	Marathon running	39.6	25	No	Yes (> 1-mo follow-up)	11 599	4.7	5.5	History of hypothyroidism, over-the-counter use of modafinil
Sanabria-Mateos et al <sup>6</sup>	Running an ultra-marathon		41	Yes	Yes (22-mo follow-up)			13	Hepatectomy with portocaval shunt before liver transplant; needed inotropic support and hemodialysis
Kurowski et al <sup>21</sup>	Intensive indoor exercise	40.5	13	No	Yes (> 2-mo follow-up)	11 000	10.5	4.0	Needed intubation; mild cerebral edema
Ramanathan et al <sup>7</sup>	Football training	40	20	Yes	Yes (1-y follow-up)	342		8.2	Required renal replacement therapy
Heneghan et al <sup>8</sup>	62-km run		40	Yes	Yes (6-mo follow-up)	4800		24	Hepatectomy with portocaval shunting before liver transplant
Chen et al <sup>20</sup>	Sitting in a hot sauna	41.7	73	No	Yes (> 20-d follow-up)	2397	11.16		History of hypertension and atrial fibrillation; needed high-volume plasma exchange
Raj et al <sup>16</sup>	2-mile jog	41.7	11	No	Yes (> 6-wk follow-up)	7090	23.4	3.15	Needed intubation, vasopressors, hemofiltration, and therapeutic plasma exchange
Azzopardi et al <sup>22</sup>	41-km run	40.8	25	No	Yes (> 3-wk follow-up)	ALT = 2912	36	1.12	Needed inotropic support
Jin et al <sup>23</sup>	Physical work	>40	35	No	Yes (> 2-mo follow-up)	1841	14.9		
Erarslan et al <sup>24</sup>	Stay in sauna for 1 h	40	63	No	Died after 6 days	3450	7.8	9.48	Needed intubation
Weigand et al <sup>2</sup>	Running half marathon		23	No	Yes (> 1-wk follow-up)	8378	40	2.8	
	Working on a hot day	42	46	No	Yes (> 23-d follow-up)	15 929	1.9	1.9	Needed hemodialysis
Kim et al <sup>17</sup>	Taking a bath for 3 h	41	68	No	Died after 25 days	2136	53	7.57	History of diabetes; needed intubation and hemofiltration
Takahashi et al <sup>9</sup>	Rugby practice	42	16	Yes (living donor)	Yes (1-y follow-up)	7410		10.5	Needed intubation up to POD26 and hemofiltration up to POD52
Hadad et al <sup>25</sup>	8-km march under heavy heat load	39.8	18	No	Yes (> 12-d follow-up)	1500	11.1	2.17	
Wagner et al <sup>26</sup>	Hard physical construction work	41.9	24	No	Yes (3-y follow-up)	3230	12.3	8.8	



**Table 1 (Continued).** Literature Search on All Published Cases of Liver Failure Associated With Heat Stroke

Reference	Activity Type	Max Temp, °C	Age, y	Liver Transplant	Survival	Peak AST, IU/L	Peak Bilirubin, mg/dL	Peak INR	Comments
Berger et al <sup>10</sup>	Football practice	41.8	16	Yes	Died on POD12	11 400	14.3		Needed hemodialysis
Giercksky et al <sup>27</sup>	5-km run		31	No	Yes	ALT = 16 410		4.2	
Ichai et al <sup>18</sup>	3-h hike	39.2	32	No	Died after 6 days	6710			Needed hemofiltration
Saissy et al <sup>11</sup>	Commando march	20	30	Yes	Died after 11 months				

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; Max Temp, maximum temperature; POD, postoperative day

chronic rejection 11 months after liver transplant.<sup>11</sup> More aggressive hemodialysis or combined kidney and liver transplant could have resulted in the control of multiorgan failure and a more successful outcome.

Our present cases and other studies have demonstrated that no criterion standard for the treatment of ALF after HS is currently available. In addition, there are no definite indications for liver transplant in the setting of HS. The decision to transplant should be considered on a case-by-case basis according to clinical presentation and progression of liver decompensation. It is crucially important that irreversible brain damage (eg, edema, stroke, and herniation) is ruled out before these patients are placed on the wait list. Long-term neurologic compromise (varying degrees of irreversible brain injury) occurs in approximately 30% of patients.<sup>12</sup>

## Conclusions

Heat stroke is a rare but a potentially fatal cause of ALF. Liver failure after HS is reversible in many cases, and conservative management can be successful even in the presence of accepted criteria for emergency liver transplant. In some cases, if the liver does not show signs of recovery despite optimal conservative treatment, liver transplant should be performed. Aggressive hemodialysis or combined kidney and liver transplant may be crucial steps to control multiorgan failure. However, the results are in general poor, and there are no guidelines for the procedure. Patients with HS-associated liver dysfunction should be closely monitored in the intensive care unit, and early communication with transplant centers might be crucial to successful management.

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