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## 1 **Liver transplantation in patients with liver failure related to exertional heatstroke**

2

3 Philippe Ichai <sup>1,2,3</sup>, Astrid Laurent-Bellue <sup>4</sup>, Christophe Camus <sup>5</sup>, David Moreau <sup>6</sup>, Mathieu  
4 Boutonnet <sup>7</sup>, Faouzi Saliba <sup>1,2,3</sup>, Jean Marie Peron <sup>8</sup>, Carole Ichai <sup>9</sup>, Emilie Gregoire <sup>10</sup>, Luc  
5 Aigle <sup>11</sup>, Julien Cousty <sup>12</sup>, Alice Quinart <sup>13</sup>, Bertrand Pons <sup>14</sup>, Marc Boudon <sup>1,2,3</sup>, Stephane  
6 André<sup>1</sup>, Audrey Coilly <sup>1,2,3</sup>, Teresa Antonini <sup>1,2,3</sup>, Catherine Guettier <sup>2,3,4</sup>, Didier Samuel <sup>1,2,3</sup>

7

- 8 1. AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Liver Intensive Care Unit,  
9 Villejuif, F-94800, France  
10 2. INSERM, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France  
11 3. DHU Hépatinov, Villejuif, F-94800, France  
12 4. APHP Hôpital Bicêtre, Department of Pathology, Le Kremlin-Bicêtre, France  
13 5. CHU de Rennes, Department of infectious disease and Intensive Care Unit, Hôpital  
14 Pontchaillou, Rennes, France  
15 6. Epidemiological Statistician, Barcelona, Spain  
16 7. Percy Military Teaching Hospital, French Ministry of Defence. Intensive Care Unit,  
17 Clamart 92000, France  
18 8. Hôpital Purpan, Department of Hepato-Gastro-Enterology, Université Paul Sabatier III.  
19 Toulouse, 31059, France  
20 9. Hôpital Saint Roch, Liver Intensive Care Unit, Nice, 06006, France  
21 10. AP-HM Hôpital La Timone, Département de chirurgie digestive, Marseille, 13005,  
22 France  
23 11. 154<sup>e</sup> Antenne Médicale du 10<sup>e</sup> Centre Médical des Armées.  
24 12. CHU de La Réunion, Intensive Care Unit, La Réunion.  
25 13. CHU de Bordeaux, Hôpital Pellegrin, Bordeaux, 33 076, France  
26 14. CHU Pointe à Pitre, Intensive Care Unit, 97159 Pointe à Pitre

27

28

### 29 **Corresponding author**

30 Philippe ICHAI, Hôpital Paul-Brousse, Centre Hépato-Biliaire, Liver Intensive Care Unit,  
31 12 Avenue Paul Vaillant Couturier - 94804 Villejuif France  
32 e-mail: [philippe.ichai@aphp.fr](mailto:philippe.ichai@aphp.fr)

33

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36 without liver transplantation; histological feature.

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PI conceived and wrote the first draft of the paper. CG and ALB performed histological reviews of all the native livers. ALB wrote the section on histology. DM provided support with biostatistics. All authors reviewed and approved the final version, and made the decision to submit the manuscript for publication.

**Abbreviations**

EH, Exertional Heatstroke; ALF, acute liver failure; sALI, severe acute liver injury; sALI/ALF-EH, sALI/ALF related to exertional heatstroke; HE, Hepatic encephalopathy; LT, liver transplantation; SU LT, Super Urgent Liver Transplantation; ELT, emergency liver transplantation; MODS, severe multi-organ dysfunction; MOF, multi-organ failure.

60 **Lay Summary**

61

62 Acute liver injury due to heatstroke can progress to acute liver failure (ALF) with organ  
63 dysfunction despite medical treatment; in such situations, liver transplantation (LT) may offer  
64 a therapeutic option. The classic criteria for LT appear to be poorly adapted to heatstroke-  
65 related ALF.

66 Our study confirmed that the first-line therapy for heatstroke leading to ALI is medication,  
67 and that LT is only rarely necessary. A decision to perform transplantation should not made  
68 hastily, even in the event of severe liver failure Account must be taken of fluctuations in PT  
69 values and the patient's clinical status. Pathological investigations of explanted livers have  
70 showed little potential for effective mitosis, with diffuse "mitonecrotic" features.

71           **ABSTRACT**

72           Severe acute liver injury (sALI) is a grave complication of exertional heatstroke (EH).  
73   Liver transplantation (LT) may be a therapeutic option, but the criteria for, and timing of  
74   transplantation have not been clearly established.

75           The aim of this study was to define the profile of patients who require transplantation  
76   in this context.

77           **Patients and Methods**

78           This was a multicentre, retrospective study of patients admitted with a diagnosis of  
79   EH-related sALI with a prothrombin time (PT) of less than 50%.

80           **Results**

81   Twenty-four male patients were studied. 15/24 patients (mean median nadir PT: 35% (29.5-  
82   40.5)) improved under medical therapy alone and survived. Nine of the 24 were listed for  
83   emergency LT. At the time of registration, the median PT was 10% (5 - 12) and all had  
84   numerous dysfunctional organs. Five patients (nadir PT: 12% (9-12)) were withdrawn from  
85   the list because of an elevation of PT values that mainly occurred between D2 and D3.  
86   Ultimately, four patients underwent transplantation as their PT persisted at < 10%, 3 days  
87   (2.75 – 3.25) after the onset of EH, and more than three organs dysfunctions. Three of these  
88   four patients were still alive one year later. Histological analysis of the four explanted livers  
89   demonstrated massive or sub-massive necrosis, and little potential for effective mitoses,  
90   characterised by a "mitonecrotic" appearance.

91  
92           **Conclusion**

93           The first-line treatment for severe ALI related exertional heatstroke is medical therapy.  
94   LT is only a rare alternative and such a decision should not be taken too hastily. A persistence  
95   of PT <10%, without any signs of elevation after a median period of 3 days since the onset of  
96   heatstroke, was the trigger adopted in order to decide upon LT.

97 Exertional heatstroke (EH) is a rare but serious complication that can occur during  
98 intense and prolonged physical exercise in a hot and humid climate. It is mainly characterised  
99 by hyperthermia higher than 40°C associated with central neurological disorders. It occurs in  
100 individuals who were previously in good health (1).

101 Liver injury is common in the context of exertional heatstroke. It is usually moderate  
102 and characterised by elevated transaminase levels. This injury is generally reversible and  
103 asymptomatic, although more rarely it may be accompanied by severe liver injury (sALI) or  
104 acute liver failure (ALF), both of which have a poor prognosis. This liver injury is clearly due  
105 to multiple factors: lesions induced by hyperthermia, hypoxia, endotoxemia, blood  
106 coagulation disorders or sepsis. It is often one symptom of severe multi-organ dysfunction  
107 (MOD) or multi-organ failure (MOF). The control of body temperature by cooling as soon as  
108 the patient is taken in charge is essential and will influence the severity of organ injury.

109 The indication for LT is not clearly established, for three main reasons. Firstly, the  
110 criteria for LT may be interfered with by the existence of a coagulation disorder (DIC) which  
111 combined with the hepatic lesions may overestimate the severity of liver failure (2).  
112 Secondly, liver failure may be reversed at the same time as the failure of other organs, using  
113 resuscitation techniques. And thirdly, only a few cases of liver transplantation have been  
114 reported, so it is not possible to clarify its indication in this context.

115 The aim of this study was therefore to define a clinical, biological, static and dynamic  
116 profile of patients in whom liver transplantation should be considered.

117

## 118 **1- PATIENTS and METHODS**

119 Between 1995 and 2016, we identified 26 patients who were admitted to seven tertiary centres  
120 with a diagnosis of EH associated with severe Severe Acute Liver Injury liver (sALI) defined  
121 by a prothrombin time (PT) <50% (at admission or during hospitalisation) or acute liver

122 failure defined by PT <50% and hepatic encephalopathy (3). The criteria for a diagnosis of  
123 exertional heatstroke and thus inclusion in our study were a core body temperature higher  
124 than 105°F (40°C) and evidence of central nervous system dysfunction (seizures or altered  
125 senses such as disorientation, delirium or coma). Out of the 26 patients initially included, two  
126 were excluded from the analysis because no data or insufficient data were available (one of  
127 these two patients died within two hours of suffering from heatstroke, with multi-organ failure  
128 including lactic acidosis, a state of shock refractory to noradrenaline, coma with a Glasgow  
129 score of 3 and respiratory distress), so that 24 patients were finally studied. All had previously  
130 been in good health. All clinical, biological and histological data (when available) were  
131 collected as from the onset of heatstroke, daily during hospitalisation in the ICU until  
132 improvement, and at the time of LT or death. The most severe biological values per 24-hour  
133 period were considered when several values were available during that period.

134 The indication for liver transplantation in patients with ALF was determined in  
135 accordance with the Clichy-Villejuif criteria (4) and/or King's College Hospital criteria (5).

136 All patients were managed at the site of their heatstroke by a mobile medical team. Patients  
137 with a Glasgow score <7 were intubated and placed under mechanical ventilation. Their mean  
138 arterial pressure was maintained above 70-75 mmHg. In patients with systemic hemodynamic  
139 instability who did not respond to volume expansion, the adjunctive use of noradrenaline was  
140 considered. Continuous venovenous haemofiltration was used for renal replacement therapy.  
141 The external temperature of patients was lowered by cooling them or medication  
142 (paracetamol). All these measures were pursued following their admission to the ICU.  
143 Patients under mechanical ventilation were sedated, and all patients received an N-acetyl  
144 cysteine regimen (6).

145 Organ dysfunction or failure (MOD or MOF) was defined using clinical, biological,  
146 electrical and ultrasound criteria (7, 8).

147 **Pathology**

148

149 The native livers of all four transplanted patients, and liver biopsies from three patients who  
150 were not listed for LT, were collected respectively 2.6 days (range, 1.7-4) and 5 days (range,  
151 2-5) after exertional heatstroke and were available for histological analysis. All seven cases  
152 were reviewed by two pathologists (ALB, CG) using a semi-quantitative assessment method  
153 as described in Appendix 1.

154

155 **Statistical analysis**

156 Continuous variables were reported as medians and 25<sup>th</sup> to 75<sup>th</sup> percentiles (Q1-Q3).  
157 Patients listed for emergency liver transplantation (super-urgent, SU) were compared with  
158 those not listed. Because the patient sample was small, the two groups were compared using  
159 non-parametric Wilcoxon or Kruskal-Wallis tests. Categorical variables were reported as  
160 percentages and compared using the  $\chi^2$  or Fisher's exact tests. A value of  $p < 0.05$  was  
161 considered to be significant.

162 Statistical analyses were performed using R Statistical Software version 3.4.0 (R  
163 Foundation for Statistical Computing, Vienna, Austria, 2015).

164

165

166 **2- RESULTS**

167

168 **2-1 Characteristics of the 24 patients with heatstroke (Table 1)**

169 All 24 patients were male, with a median age of 27.5 years (25.0-37.6). All had previously  
170 been in good health and were athletes. Ten were career military personnel and four were  
171 completing their military service. Heatstroke occurred in all patients between April and  
172 October in very hot conditions following vigorous exercise (jogging, marathon, half-  
173 marathon, "iron man" race, training run or commando march) and if they had been racing they  
174 reached the finish line. The median distance travelled before the onset of heatstroke was 10  
175 km (8-15).

176 Their median body temperature was 40.7°C (40.0-41.4). All patients presented with  
177 incipient neurological signs: six with convulsive seizures then coma (25%); 14 (58%) with  
178 initial coma and four with confusion (17%). The median Glasgow score at the arrival of the  
179 mobile medical team was 7 (3-10). Twelve patients (50.0%) were placed under mechanical  
180 ventilation because of consciousness disorders. Nine patients (37.5%) presented with signs of  
181 mesenteric dysfunction that manifested itself in the form of diarrhoea. All patients received  
182 large quantities of intravenous fluids (glucose, physiological saline and/or Ringer's lactate  
183 solution). Six patients (25.0%) presented initially with collapse that was reversible after  
184 vascular filling with macromolecules (n=2) and the administration of noradrenaline (n=4).

185 Immediately after the heatstroke, the body temperature was lowered by external cooling using  
186 ice packs placed on the vascular axes and by the intravenous infusion of refrigerated fluids.  
187 Five patients received paracetamol (between 1 and 2 grams in total). The median delay  
188 between the onset of heatstroke and transfer to a tertiary centre was 0 day (0-1).

189 After admission to the ICU unit, cooling was pursued and supplemented with a fan and a  
190 hypothermic blanket. The median body temperature measured at admission to the ICU had

191 fallen to 38.7°C (38.4-39.1). A brain scan was performed in 14 patients (58.5%) and the  
192 findings were normal. When performed, an analysis of the cerebrospinal fluid was normal  
193 (n=7). Twenty-two patients (92%) presented with renal damage, 19 (79%) with  
194 rhabdomyolysis, seven (29%) with biological pancreatitis, ten (42%) with myocardial injury,  
195 five (21%) with haemodynamic instability, and four (17%) with ARDS. All developed  
196 sALI/ALF after their admission to hospital. The median SAPS 2 (Simplified Acute  
197 Physiology) score at admission to the ICU was 29 (17-48.5).

198 The median values at ICU admission with respect to PT, Factor V, INR and total  
199 bilirubin were 70.5% (55.25-82.75), 75% (52-84.5), 1.2 (1.1-1.6) and 14 µmol/l (10-20.75),  
200 respectively.

## 201 **2-2 Clinical outcomes**

203

### 204 *2-2-1 Candidates for liver transplantation (n=9)*

205 Nine (37.5%) of the 24 patients with heatstroke were listed for LT on a super urgent  
206 basis. The demographic, clinical and biological characteristics of these patients at and after  
207 admission and listed or not for super-urgent (SU) LT are shown in Table 1. At the time of  
208 heatstroke, the two groups of patients (listed or not for SU LT) were similar in terms of their  
209 demographic characteristics, Glasgow score, blood pressure, collapse and heart rate (Table 1).  
210 The median nadir PT value in the 15 non-listed patients was 35% (29.5-43.5). The median  
211 period elapsing between heatstroke and registration on the waiting list was 3 days (2-3). At  
212 the time of listing, six patients were placed on mechanical ventilation and sedated, five  
213 required haemodynamic support, five with renal failure received renal replacement therapy  
214 (continuous venovenous haemofiltration) and five were treated with albumin dialysis  
215 (GAMBRO® (Lund, Sweden). All nine patients presented with signs of DIC (Table 2). Five  
216 of the nine listed patients received fresh frozen plasma. The median values at the time of

217 listing for SU transplantation with respect to PT, Factor V, bilirubin, ALT and creatinine were  
218 9% (5-13), 12% (4-14), 90  $\mu\text{mol/l}$  (65-119), 6500 IU/L (5200-10000) and 155 $\mu\text{mol/l}$  (104.8-  
219 321.8), respectively.

220 Between H0-24 (D1) and H96-120 (D5), PT levels were significantly lower among  
221 listed patients, while after D2 bilirubin was significantly higher (Figure 2A, 2B). In the same  
222 patients after H0-24, the platelet counts were significantly lower, while AST and ALT values  
223 were significantly higher after H24-48 (data not shown).

224 Between H0-24 (D1) and H48-72 (D3), PT levels fell more (>70%) in listed patients than in  
225 those not listed; in the latter, the reduction was not only less marked but a rise was seen  
226 between D2 and D3 (from -51% to +73%) (data not shown).

227

228 *2-2-2 Patients who were transplanted (n=4): Table 2, Figure 3*

229 Four of the nine listed patients (44.5%) underwent LT. The median periods elapsing  
230 between the onset of heatstroke and registration for SU LT among transplanted and non-  
231 transplanted patients were 1.5 days (1-2.25) and 3 days (3-3), respectively ( $p=0.040$ ). At the  
232 time of SU registration, the median PT and platelet values were lower than those seen in non-  
233 transplanted patients ( $p<0.07$ , Wilcoxon non-parametric test). The median serum ammonia  
234 level at admission was 70 $\mu\text{mol/l}$  (62-233) ( $N<45$ ). The median period elapsing between  
235 heatstroke and liver transplantation was 3 days (2.75-3.25). At the time of transplant surgery,  
236 three of the four patients were ventilated, one required haemodynamic support  
237 (noradrenaline), and two were under continuous veno-venous haemofiltration and receiving  
238 liver support (MARS®). Three of the four patients were administered fresh frozen plasma  
239 prior to transplantation. The median PT values at H24-36, H36-48 and H48-60 in transplanted  
240 patients (9%; 5% and 5%, respectively) were lower than those of SU-registered patients who  
241 were not transplanted (18%, 13% and 11%, respectively) ( $p<0.2$ ) (Supplementary Table 2). At

242 the time of LT, median total bilirubin, PT, Factor V, ALAT and creatinine values were 84.5  
243  $\mu\text{mol/L}$  (range, 66-118), 7.5% (range, 5-17), 10% (range: 1-15), 6970 IU/L (range, 5003-  
244 15752) and 401 $\mu\text{mol/L}$  (range, 178-457), respectively. The nadir PT value in non-  
245 transplanted patients was 12% (9-12) and rose as from H60-72 in 2 patients, H72-84 in 2  
246 patients and H84-96 in 1 patient. Transplanted patients presented with low bilirubin values  
247 (lower than 20  $\mu\text{mol/l}$ ) at admission, and then a marked elevation was seen at D3 (rising by  
248 more than 200%).

249

### 250 **2-3 - Survival**

251

252 The overall survival rate among patients presenting with heatstroke-related ALI/ALF was  
253 96%. Survival rates without transplantation and after transplantation were 100% and 75%,  
254 respectively. One of the transplanted patients died at 11 months, two months after re-  
255 transplantation for chronic rejection. All patients not listed for SU LT recovered their normal  
256 liver function and were discharged from hospital, and none of them presented with any after-  
257 effects. The median ICU and hospital length of stay of patients not listed and listed for SU LT  
258 were 3.0 days (2.0-6.7) and 10.0 days (5.0-12.8), and 17.3 days (10.0 - 26.0) and 34.3 days  
259 (26.0 - 62.0), respectively.

260

### 261 **2-4 - Histological findings (Table 3, Figure 4)**

262

263 The livers of the transplanted patients were not atrophic. The cut surface, when depicted, was  
264 generally yellowish and soft, suggesting steatosis.

265 All native livers displayed a normal architecture without any portal fibrosis. The portal tracts  
266 contained a mild inflammatory infiltrate without significant periportal activity. The bile ducts  
267 were present, occasionally with non-destructive lymphocytic or neutrophilic cholangitis.

268 There was a constant intraportal cholangiolar reaction with frequent acute neutrophilic  
269 cholangiolitis. Massive coagulation lobular necrosis was always observed in the centrilobular  
270 and mediolobular areas (zones 3 and 2), sparing only a few hepatocellular plates around the  
271 portal tracts. Lobular necrosis affected 60% to 90% of the hepatic parenchymal surface. This  
272 hypoxic necrosis was accompanied by a moderate macrophage cleansing reaction. The  
273 remaining hepatocytes were frequently clarified and swollen. In one case patient (n°4), a  
274 periportal ductular reaction was observed at the interface with the damaged hepatic  
275 parenchyma. Steatosis was present and involved 5% to 90% of hepatocytes, sometimes visible  
276 within the necrotic area. Steatosis was both macro- and microvacuolar. Mild lobular  
277 inflammation was seen in three of the four native livers (lymphocytes, sometimes with  
278 neutrophils). The mitotic count within the remaining hepatocytes was high (17 to 82 mitoses  
279 for 10 HPF) and these mitoses were highlighted by Ki-67 immunostaining. However, these  
280 mitotic figures always displayed a very peculiar aspect of chromosomal material dispersion  
281 giving them a mitonecrotic appearance.

282 The lesions observed in the three liver biopsies from non-transplanted patients (n=3), were by  
283 contrast less severe. The portal tracts contained a mild inflammatory and cholangiolar  
284 reaction in only one case. The same patient displayed centrilobular coagulation necrosis  
285 affecting 15% of the hepatic parenchymal surface. Only sparse necrotic hepatocytes were  
286 visible in the two other cases. Hepatocytes were frequently clarified and swollen (in 25% to  
287 80% of cases). Steatosis was present and involved 5% to 15% of hepatocytes. The mitotic  
288 count was less remarkable (1 to 11 mitoses for 10 HPF) but the mitotic figures had the same  
289 mitonecrotic appearance.

290

291

### 292 3- DISCUSSION

293 One of the serious complications of heatstroke is the onset of multi-organ dysfunction  
294 (MOD) or failure (MOF), which notably includes ALI or ALF. The spontaneous prognosis of  
295 EH-related ALF may be poor. If there is no improvement in liver function, liver  
296 transplantation may offer a therapeutic option. The KCH (non-paracetamol) and Clichy-  
297 Villejuif criteria appear to be poorly adapted to HE-related ALF (4, 5). One of the principal  
298 prognostic factors included in these criteria is hepatic encephalopathy, which together with  
299 initial and constant neurological dysfunction in the context of heatstroke may become  
300 superimposed and make it difficult to distinguish one from the other. The determination of  
301 arterial ammonia levels, and the monitoring of electrical activity by an electroencephalogram,  
302 may help to make a distinction between these two mechanisms (9, 10). Furthermore, many of  
303 these patients require mechanical ventilation and sedation, which adds a further element of  
304 confusion. The distinction between ALI and ALF is therefore very unclear and the severity of  
305 liver failure may be overestimated. In our series, 12 patients were ventilated and sedated at  
306 admission, six at the time of registration on the transplant list and three at the time of LT.  
307 Thus removal from the waiting list of three of the six listed patients coincided with their  
308 extubation.

309 A second element that may distort a decision concerning liver transplantation is the  
310 onset of disseminated intravascular coagulation (DIC) and/or fibrolysis. These coagulation  
311 abnormalities develop as from the onset of heatstroke (11). A normalisation of body  
312 temperature can inhibit fibrolysis. On the other hand, DIC persists and may exacerbate the  
313 drop in prothrombin activity, which could lead to an emergency listing that is too early and  
314 incorrect (12-14). This was probably the case in some of our patients who were listed for SU  
315 LT but not transplanted. Thus it is above all the evolving dynamics of the patient that will  
316 enable a decision regarding an indication for LT.

317 This series of 24 patients with sALI/ALF-EH highlighted several points: (1) 20/24  
318 (83%) patients presented a severe form of liver injury, associated or not with the dysfunction  
319 of one or more other organs, and improved under medical therapy alone. Five of them,  
320 initially listed for liver transplantation, were subsequently removed from the list because of an  
321 improvement in their liver function. The median nadir PT of these patients was 12% (9-12).  
322 Survival without transplantation reached 100% and they all recovered normal liver function;  
323 (2) 4/24 (16.5%) patients were transplanted as an emergency. Their median PT value at the  
324 time of transplantation was <10%, 2 to 4 days after suffering from heatstroke, and at least four  
325 of their organs were dysfunctional. Their survival a year after liver transplantation reached  
326 75%. Finally (3), the histological analysis of all native livers from transplanted patients  
327 revealed massive or sub-massive hepatocyte necrosis and inefficient mitoses.

328

329 Three evolving profiles could be seen among our patients who presented with severe  
330 liver injury related to heatstroke.

331 The first corresponded to patients with moderate liver injury who started to improve as from  
332 D2; in most cases, no other organs were affected by the heatstroke. The liver function of these  
333 patients improved rapidly without transplantation being envisaged or discussed. This profile  
334 does not generally pose any decision-making problems.

335 The second profile corresponded to patients with liver injury that was more severe, persisted  
336 or continued to worsen significantly after D2 (PT <20%). Most of them were suffering from  
337 other organ dysfunctions and usually required organ support (haemodynamic, replacement  
338 renal therapy, mechanical ventilation). However, only four of them were transplanted. The  
339 other five improved under medical treatment. Analysis of the kinetics of prothrombin levels  
340 identified minimal but unquestionable differences between these two groups of patients, such  
341 as a persistence of PT<10% in the patients scheduled for transplantation until the surgical

342 procedure, without any initiation of elevation, and the start of an elevation of prothrombin  
343 levels in patients who survived without transplantation, mainly between H60 and H72. So  
344 there was a possible chance of recovery without transplantation, even in the case of major  
345 hepatic failure, thus clearly underlining the need for any decision on transplantation not to be  
346 hasty. Inversely, the lack of even a minimal improvement required the indication of LT in  
347 these patients, who also presented with the dysfunction or failure of other organs. In the  
348 literature, most patients presenting with EH-related ALF died; either they were not  
349 transplanted or they were transplanted too late, after D4-D6 (15-21). Thus the probability of  
350 an improvement without LT seems to diminish after that period and any decision regarding  
351 liver transplantation must be envisaged before that time point.

352 A third profile can be seen from the literature. These are patients who present with heatstroke  
353 involving the very rapid installation of non-reversible MOF that causes the patient's death  
354 within a very short time after its onset (within 48 hours) (22). This was the case of one of the  
355 two patients excluded from our study, who died within 2 hours of heatstroke from multi-organ  
356 failure.

357

358 Heatstroke-related histological lesions affecting the liver (swelling, clarification,  
359 vacuolization, steatosis and massive centrilobular necrosis) are probably the consequence of  
360 two separate mechanisms (13, 21, 23-27): the direct effects of heat and hepatic hypoxia  
361 (hepatic hypoperfusion, cardiac failure). This liver damage, which in some cases may be  
362 extremely severe, gives rise to hepatocyte regeneration and cholangiolar reaction. Massive  
363 coagulation necrosis confirmed the severity of liver injury in our four transplanted patients  
364 and added a further retrospective argument in favour of transplanting for these patients.  
365 Mitoses were numerous in all native livers and less frequent in the liver biopsies obtained  
366 from three other patients. They had an abortive appearance that has not been described until

367 now in the relevant literature. The positivity of these figures for Ki-67 led us to think that they  
368 were mitoses rather than karyorrhexic nuclei. However, their appearance suggested that they  
369 would be inefficient in terms of hepatocellular regeneration. This impression was reinforced  
370 by the fact that the condition of none of the four transplanted patients improved spontaneously  
371 before surgery. These abortive mitoses, to our knowledge rarely observed in other types of  
372 hepatitis (infectious, autoimmune, toxic), might have been another adverse effect of  
373 heatstroke. A liver biopsy in patients with severe acute liver injury and failure caused by  
374 exertional heatstroke can provide interesting and reliable information on the extent of liver  
375 necrosis and the number of hepatocellular mitoses. However, only three patients were  
376 biopsied during our study, at a different time in the course of their disease, and none of these  
377 three patients ultimately required a liver transplantation. Moreover, none of the four patients  
378 transplanted during this study underwent a liver biopsy prior to liver surgery. We cannot  
379 therefore deduce from this study alone a histological threshold regarding the extent of  
380 necrosis or number of mitoses that might help to predict the outcomes of such patients.  
381 Therefore, we cannot yet recommend the systematic use of liver biopsies in patients with  
382 severe acute liver injury and failure as a helpful tool to select patients who are in need of liver  
383 transplantation.

384

385         Auxiliary liver transplantation may constitute an alternative to a conventional, whole  
386 liver transplant. If the native liver can subsequently regenerate, this has the advantage of  
387 enabling the withdrawal of immunosuppressive medications. However, the procedure is more  
388 lengthier and the graft is smaller, which means that this technique should be reserved for  
389 carefully selected patients (28-30). One of our transplanted patients appeared to be in a less  
390 serious state (not ventilated, no haemodynamic failure and low-grade hepatic  
391 encephalopathy); this option was discussed but not retained for logistical reasons. Subsequent

392 histological findings on the native liver revealed the appearance of abortive mitoses  
393 (mitonecrotic aspect) which could have compromised regeneration of the native liver in the  
394 event of auxiliary liver transplantation.

395

396         The role of liver support in patients with severe hepatic dysfunction or ALF has not yet  
397 been clearly established. Several non-controlled studies have suggested the value of MARS in  
398 patients presenting with ALF (31). However, the FULMAR controlled, randomised study  
399 comparing standard treatment versus standard treatment plus MARS in patients with ALF  
400 awaiting LT was not able to conclude as to the usefulness of MARS in terms of survival at 6  
401 months. The principal explanation was the short period elapsing between randomisation and  
402 the proposal of a compatible graft (16.2 hours), which prevented evaluation of this system  
403 (32). Despite the fact that this system has not proved its impact on survival, it nevertheless  
404 forms part of our therapeutic strategy when managing these patients. Thus, in our series, five  
405 of the nine patients listed for SU transplantation received support of the MARS® type. Three  
406 of them improved and two underwent transplantation.

407

408         Although the present study was able to better comprehend patients with exertional  
409 heatstroke requiring liver transplantation (or potentially qualifying for transplantation in the  
410 future), it did have certain objective limitations.

411         The first and principal limitation of this study was that it was not possible to affirm that the  
412 transplanted patients might not have improved without this surgery. The persistence of a  
413 median PT <10% a median of 3 days after heatstroke led us to opt for transplantation.  
414 However, this value cannot be retained as the only criterion for LT, particularly since two of  
415 the five patients listed but not transplanted had PT values below the 10% threshold before  
416 they started to rise and normalise. Thus an improvement in liver function is possible, and a

417 decision on LT must not be taken hastily. The severity of clinical status, marked by the  
418 presence of several organs affected by heatstroke and requiring different types of support, and  
419 the absence of any improve in PT values were also key elements in the decision for LT. The  
420 massive hepatocyte necrosis observed retrospectively during histological studies of the native  
421 livers reinforced the approach adopted with respect to transplantation. However, further  
422 studies are necessary to validate these results.

423 The second limitation of this study mainly concerned the selection of patients. This was a  
424 retrospective, non-consecutive and probably non-exhaustive study where the impact of liver  
425 failure on prognosis could have been biased. So as to be as exhaustive as possible, all patients  
426 presenting with heatstroke-related sALI/ALF and listed for LT during the study period were  
427 screened via the Agence de la BioMedecine, and the principal tertiary centres dealing with  
428 this type of pathology were contacted.

429 The final limitation concerned the administration of fresh frozen plasma in three of the four  
430 patients listed for SU LT and subsequently transplanted, which overestimated their PT values.  
431 The routine use of fresh frozen plasma should be limited to specific situations, such as  
432 invasive procedure or active bleeding (33, 34).

433 However, at the time of SU registration, and despite this transfusion, the patients listed for  
434 transplant presented with more severe liver failure than those who were not transplanted, with  
435 a statistical tendency towards significance. This therefore reinforced our findings.

436

## 437 **Conclusion**

438 Heatstroke involving severe liver injury, associated or not with the dysfunction of  
439 other organs, improves in more than 80% of cases with medical therapy alone. An  
440 improvement in liver function is possible, even with low prothrombin values. Liver  
441 transplantation only represents a rare alternative, and achieves good survival rates after

442 surgery. However, the decision to transplant should not be taken hastily and must take  
443 account of the kinetics of PT and of the patient's clinical status. The peculiar histological  
444 features observed on all explanted livers and the aspect of abortive mitoses in hepatocytes  
445 could be attributed to the effects of heatstroke and help explain the severity of transplanted  
446 patients. However, given that only a few patients were biopsied, we cannot yet recommend  
447 liver biopsy to help select the patients who would require liver transplantation.

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- 540

541 **LEGENDS TABLES AND FIGURES**

542

543 **Table 1: Clinical and biological characteristics of patients immediately after the onset of**  
544 **heatstroke and following admission to the ICU**

545

546 Comparisons of clinical and biological values on the day of heatstroke following admission  
547 for emergency care (Wilcoxon non-parametric test).

548 \* the most severe value during the 24-hour period

549 Abbreviations: PT, prothrombin time, AST, aspartate aminotransferase; ALT, Alanine

550 aminotransferase; CPK, creatine phosphokinase; MARS, Molecular adsorbent recirculating

551 system; SAPS 2, Simplified Acute physiology Score 2

552

553 **Table 2: Principal clinical and biological characteristics of patients registered for SU**  
554 **LT, whether they were transplanted or not**

555

556 **Abbreviations:** HE, hepatic encephalopathy; MV, mechanical ventilation; RTT, renal  
557 replacement therapy; MARS, Molecular adsorbent recirculating system;

558 PT, prothrombin time, TB, total bilirubin; AST, aspartate aminotransferase; ALT, Alanine

559 aminotransferase; CPK, creatine phosphokinase; SU, super urgent (transplantation); KCH

560 criteria, King's College Hospital criteria

561 +, presence of Soluble complexes

562 \*  $p < 0.07$ , (p value comparison using the Wilcoxon test between SU LT and SU non-LT  
563 patients)

564 \*\*  $p < 0.40$

565

566

567 **Table 3: Summary of pathological findings**

568 NA: not available, Ly: lymphocytes, N: neutrophils, MaV: macrovesicular, MiV:  
569 microvesicular, HPF: High-Power Fields.

570

571 **Figure 1: Study flow diagram**

572

573 **Figure 2: Prothrombin Time (a) and Total bilirubin (b) from day 1 to day 5 as a**  
574 **function of patient status (SU patients and non-SU patients)**

575 n1, number of non-SU patients; n2, number of SU patients;

576 \* p<0.05; \*\* p<0.01 (p value of daily comparisons using the Wilcoxon test between SU and  
577 non-SU patients; ns, not significant

578

579 **Figure 3: Prothrombin Time (a) and total bilirubin (b) from day 1 to day 5 in patients listed**  
580 **for LT and as a function of patient status (transplanted and non transplanted patients)**

581 SU patients, super-urgent patients

582 SU LT patients, super-urgent liver transplantation patients

583

584 **Figure 4**

585 **Figure 4A** (HES, x200, patient n°2): massive coagulation lobular necrosis (zones 2 and 3,  
586 arrow), note the thin rim of hepatocytes around the portal tract (star), the absence of  
587 inflammatory cells within the necrosis and the cholangiolar portal reaction.

588 **Figure 4B** (HES, x400, patient n°2): abortive mitoses around a portal tract (arrows).

589

590 **SUPPLEMENTARY TABLE**

591

592 **Supplementary Table 1: Course of PT and total bilirubin levels after Day 0**

593 \*H0: heatstroke

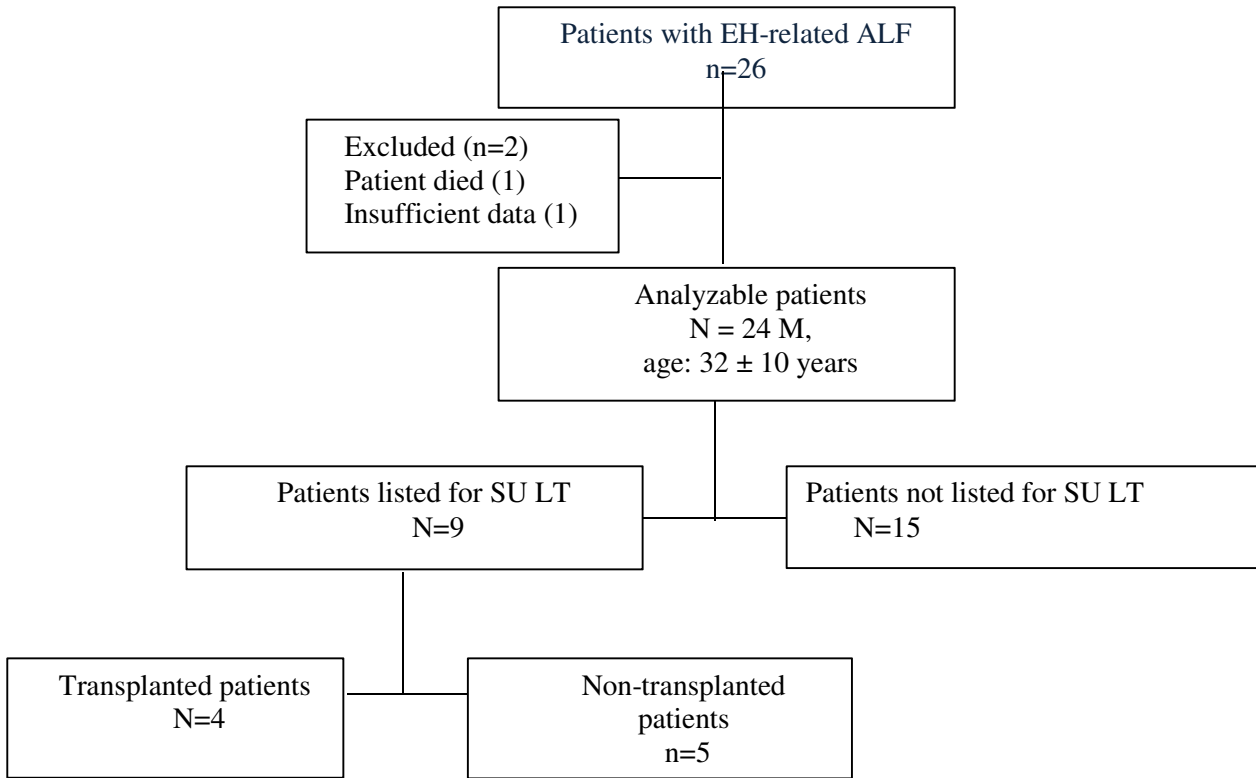
594 The data are presented as medians.

595

596 **Supplementary Table 2: Course of PT after H 0 in patients listed for LT (n=9)**

597 The data are presented as medians.

**Figure 1: Study flow diagram**



**Figure 2: Prothrombin Time (A) and Total bilirubin (B) from day 1 to day 5 as a function of patient status (SU patients and non SU patients)**

Fig 2a

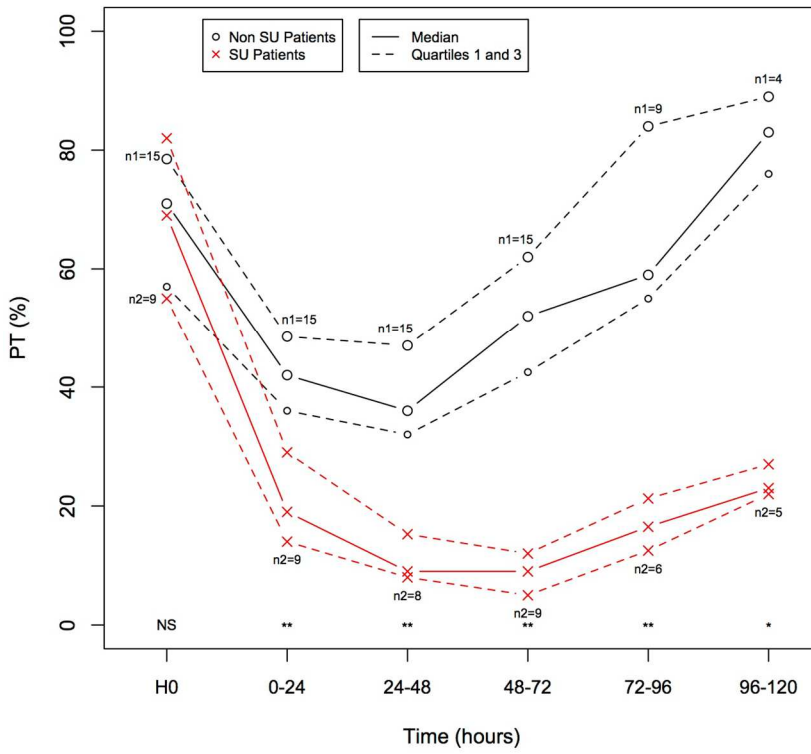
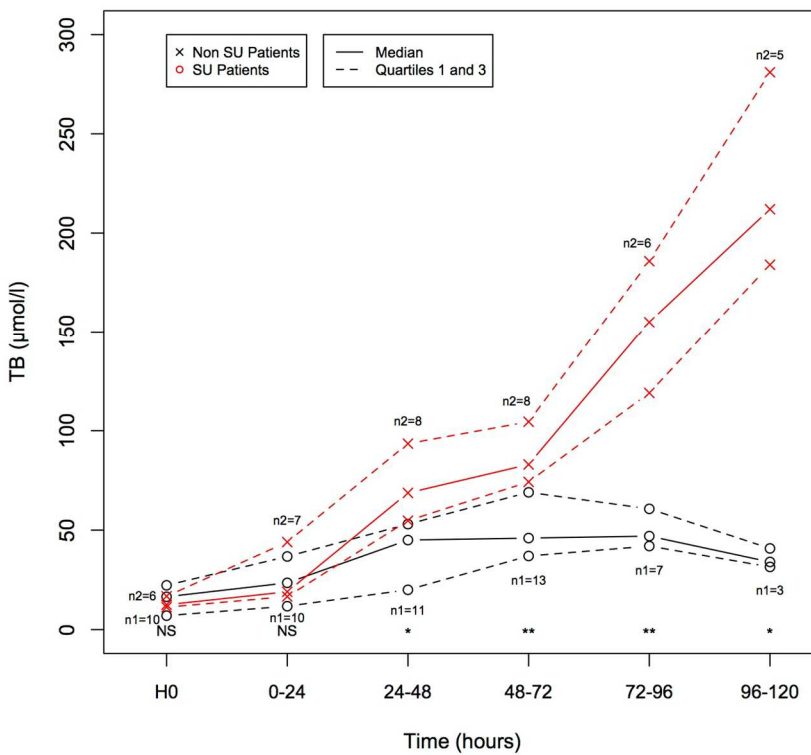


Figure 2b



**Figure 3:** Prothrombin Time (a) and Total bilirubin (b) from day 1 to day 5 in patients listed for LT and as a function of patient status (transplanted and not transplanted patients)

Figure 3a

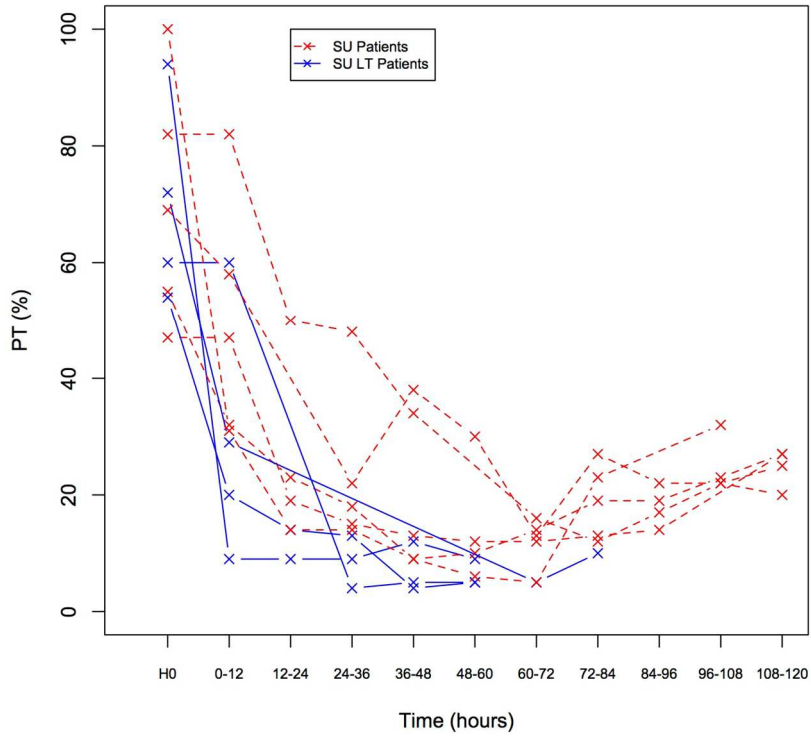


Figure 3b

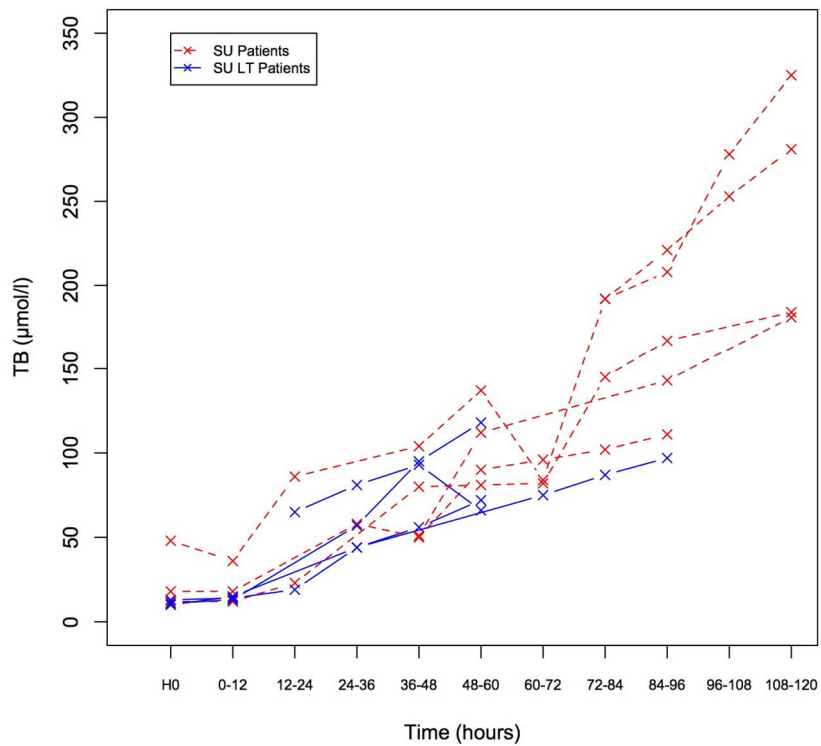


Figure 4A (HES, x200, case n°2)

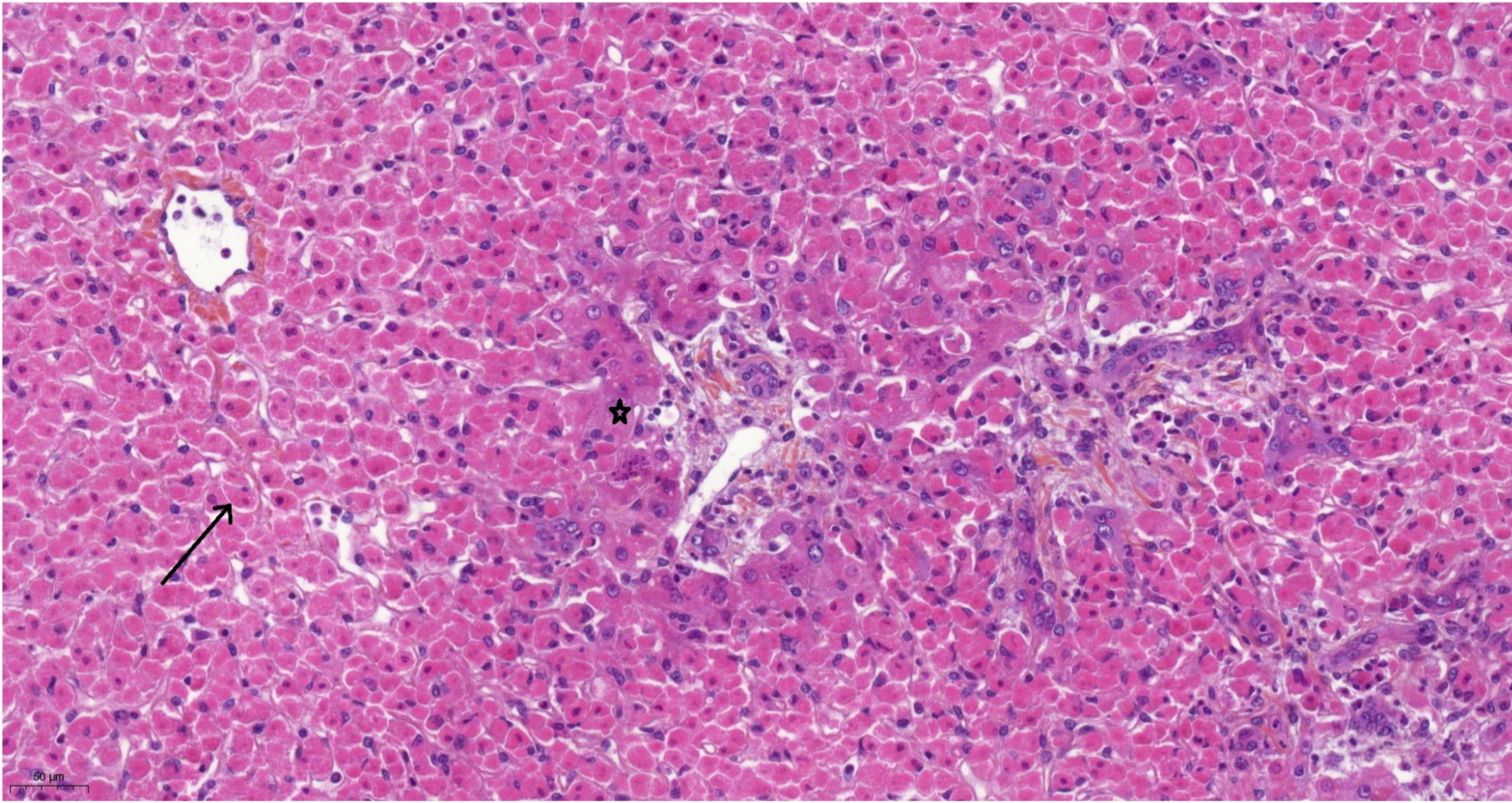
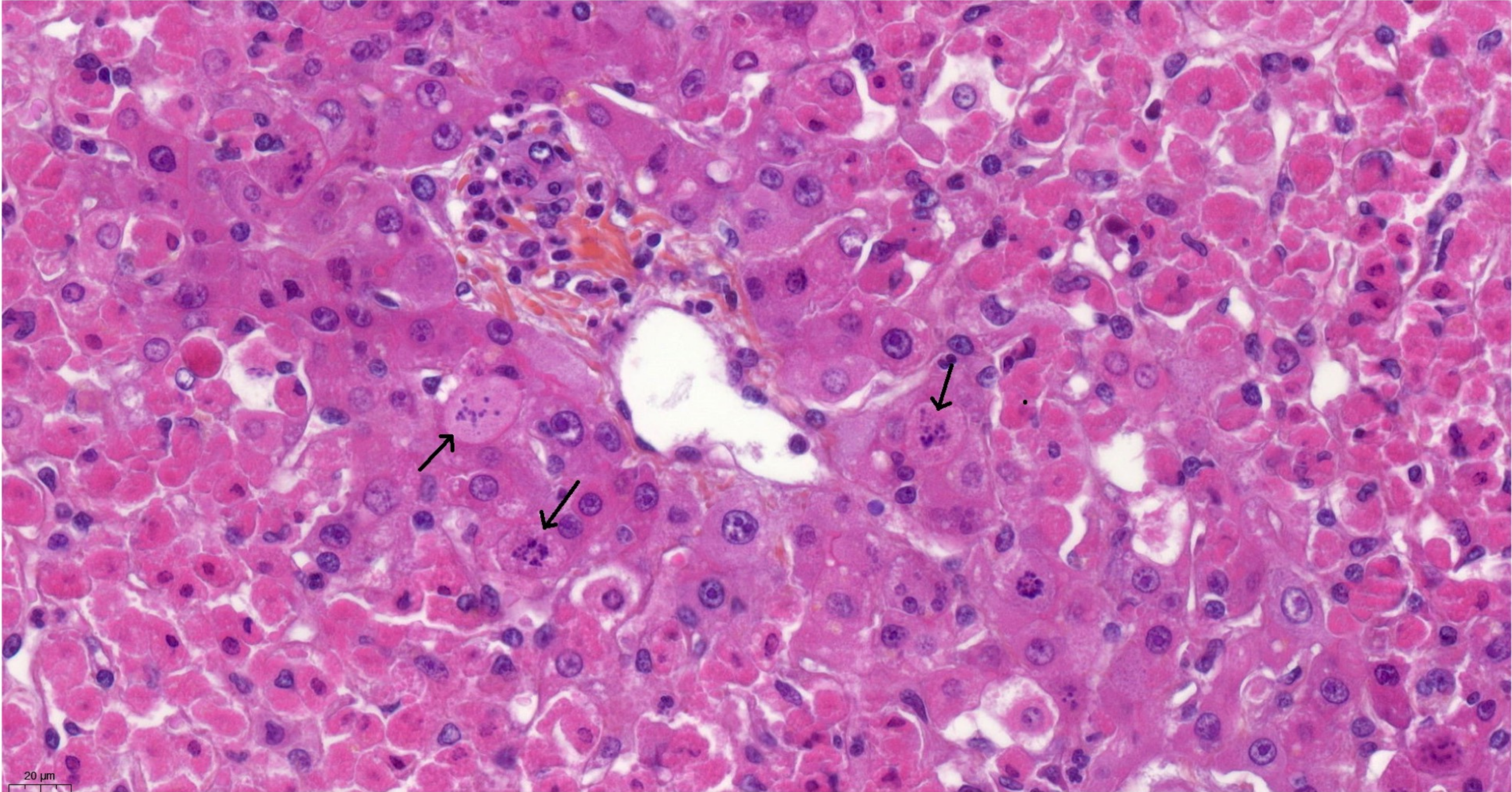


Figure 4B (HES, x400, case n°2)



**Table 1: Clinical and biological characteristics of patients immediately after the onset of heatstroke and following admission to the ICU**

	Total (n=24)	Patients listed for SU LT (n=9)	Patients not listed for SU LT (n=15)	p
Age (years)	27.5 (25.0-37.6)	28.2 (26.2-37.3)	26.3 (24.9-37.0)	ns
Initial Body temperature	40.7 (40.0-41.4)	41 (40.0-42.0)	40.0 (40. -41.0)	ns
Glasgow score in the field	7 (3-10.25)	6 (3-7)	7 (4.0-12.5)	0.19
Heart rate in the field	150 (130-160)	155 (141-66,2)	140,0 (130,0-160,0)	ns
Systolic blood pressure (mmHg)	100.5 (80-121,2)	84 (75-120)	106 (90-117.5)	ns
Diastolic blood pressure (mmHg)	50 (40 - 64,25)	45 (40-60)	50 (44.5-64.5)	ns
Collapse (Yes)	25.0 (6)	44.4 (4)	13,3 (2)	0,15
<b>Initial test (H0)</b>				
PT (%)	70 (55.75 - 82)	69 (55 - 82)	71 (57- 78.5)	ns
Total bilirubin (µmol/l)	14 (10-20.75)	12.5 (11.25-16.75)	16.5 (7-22.25)	ns
AST (IU/L)	57.4 (32.5-119.5)	65 (38.5-267.5)	51 (31- 80)	ns
ALT (IU/L)	37.5 (23.75-74.5)	39 (34-78)	29 (23-52)	ns
Creatinine (µmol/l)	173.5 (157.2-181.8)	173 (156.2-193.2)	173.5 (158.2-180.8)	ns
Urea	7.3 (6.46 - 9.76)	7.6 (6.58-8.85)	7.3 (6.14- 10.1)	ns
CPK (µmol/l)	526 (271-1870)	476 (255.5-1197)	526 (284- 1870)	ns
Troponine (IU/L)	0.81 (0.19-1.52)	2.4 (1.54-4.3)	0.35 (0.16-1.04)	<b>0.055</b>
Lipase (IU/L)	55 (31.5-75.25)	73 (51.5-131.5)	41 (31-72.5)	ns
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	178 (126.5-211.5)	132 (112-178.5)	189.5 (143.2-216.5)	0.17
pH	7.32 (7.29-7.36)	7.29 (7.29-7.38)	7.32 (7.29-7.35)	ns
HCO <sub>3</sub> <sup>-</sup>	20 (18.1-21.75)	19 (17.25-21.5)	20.25 (18.85-21.25)	ns
Lactate (IU/L)	2.7 (2.3-4.1)	2.7 (2.23-3.08)	2.7 (2.55-4.8)	ns
SAPS II	29 (17-48.5)	<b>60 (36-71)</b>	<b>23.5 (15-28.5)</b>	<b>0.008</b>
<b>Extra-hepatic involvement after HE</b>				
Cardiac involvement (yes) *	41.7 (10)	55.6 (5)	33.3 (5)	ns
Pancreatic involvement (yes) *	29.2 (7)	<b>55.6 (5)</b>	<b>13.3 (2)</b>	<b>0.061</b>
Muscle involvement (yes) *	79.2 (19)	66.7 (6)	86.7 (13)	ns
Renal involvement (yes)*	91.7 (22)	88.9 (8)	93.3 (14)	ns
Mesenteric injury (yes)*	37.5 (9)	<b>66.7 (6)</b>	<b>20.0 (3)</b>	<b>0.036</b>
Neurological involvement	54.5 (12)	<b>88.9 (8)</b>	<b>30.8 (4)</b>	<b>0.011</b>
<b>Organ support</b>				
Renal dialysis (yes)*	20.8 (5)	55.6 (5)	0 (0)	0.003
MARS (yes)*	20.8 (5)	55.6 (5)	0 (0)	0.003
Haemodynamic support (yes)*	20.8(5)	44.4 (4)	6.7 (1)	0.047
Mechanical ventilation (yes) *	50.0 (12)	<b>88.9 (8)</b>	<b>26.7 (4)</b>	<b>0.009</b>

The data are presented as medians (Q<sub>1</sub>-Q<sub>3</sub>, first quartile - third quartile), \* % (n)  
Continuous variables were compared between the groups using the non-parametric Wilcoxon test and categorical variables using Fisher's exact test.

**Table 2: Principal clinical and biological characteristics of patients registered for SU LT, whether they were transplanted or not**

	At the time of SU registration			At the time of LT (n=4)
	All patients (n=9)	Non-transplanted patients (n=5)	Transplanted patients (n=4)	
EH (yes)	9	3	4	4
VM	6	3 (60%)	3 (75%)	3 (75%)
Sedation	6	3 (60%)	3 (75%)	3 (75%)
Inotrope +	5 (55%)	3 (60%)	2 (50%)	1 (25%)
EER	5 (67%)	4 (80%)	1 (25%)	-
MARS+EER	5 (55.5%)	3 (60%)	2 (50%)	2 (50%)
TP (%)	10 (5 - 12)	12 (12 - 13)*	6.5 (4 - 9.25)	7.5 (5-13.5)
BT (μmol/l)	97 (84 - 111)	102 (90 - 112)	81 (59.75 - 100.5)	95 (82.5 - 107.5)
AST (IU/L)	5361 (4494 - 10077)	5361 (4540 - 5986)	7286 (4368 - 12596)	7852 (5718 - 15353)
ALT (IU/L)	7854 (6394 - 10969)	8070 (6394 - 10969)	7196 (5880 - 9476)	7594.5 (5512 - 12460)
Creatinine (μmol/l)	168 (147 - 323)	168 (101 - 281)	238.5 (149.2 - 406.8)	178 (106 - 401)
CPK (μmol/l)	10639 (4116 - 65318)	10639 (4658 - 51551)	19450 (4116 - 106683)	19311 (4470 - 177835)
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	36 (33 - 47)	47 (39 - 51)	33 (30.75 - 34.5)	29.5 (26.5 - 42.5)
Delay between SU and CCE	3 (2 - 3)	3 (3 - 3)**	1.5 (1 - 2.25)	-
Delay between CCE and LT	-	-	-	3 (2.75 - 3.25)
KCH criteria	8/9	4/5	4/4	4/4
Clichy-Villejuif criteria	6/9	3/5	3/4	3/4

\* p <0.07

\*\* p=0.040

**Table 3: Summary of pathological findings**

Patients	LT	Delay HE-Biopsy	Portal fibrosis	Portal inflammation	Cholangitis	Cholangiolar reaction	Steatosis Type	Steatosis %	Lobular necrosis Topography	Lobular Necrosis %	Hepatocellular clarification and swelling %	Lobular inflammation	Mitotic count (/10 HPF)	Cholestasis
N°1	Yes	1,7	0	Mild: Ly, N	+	+	MaV and MiV	10 (within necrosis)	Confluent, zones 2 and 3	85	5	Mild: Ly, N	19	0
N°2	Yes	2.3	0	Mild: Ly, N	+	+	MaV and MiV	5 (within & outside necrosis)	Confluent, zones 2 and 3	80	5	0	82	0
N°3	Yes	3	0	Mild: Ly, N	+	+	MaV and MiV	80 (within necrosis)	Confluent, zones 2 and 3	90	5	Mild: Ly	37	0
N°4	Yes	4	0	Mild: Ly, N	+	+	MaV and MiV	90 (within & outside necrosis)	Confluent, zones 2 and 3	60	20	Mild: Ly, N	17	+
N°5	No	5	0	0	0	0	MaV and MiV	15	Sparse	1%	30	Mild: Ly	1	0
N°6	No	5	0	Mild: Ly, N	0	+	MiV	5 (within & outside necrosis)	Confluent Zone 3 + sparse	15%	25	Moderate: Ly, N	4	0
N°7	No	2	0	0	0	0	MaV and MiV	5	Sparse	1%	80	Mild: Ly, N	11	+

**Patients with Acute Liver Injury-related Heatstroke (n=24)**

Median delay between heatstroke and listing for LT: 3 days (2-3)

**Not a candidate for emergency LT (n=15)**  
Prothrombin time (median, nadir, %): 35 (29.5-43.5)

**Candidate for LT (n=9)**

At listing [ Prothrombin time (median): 10% (5-12)  
and dysfunction/failure of >3 organs

Median delay from listing to LT: 1 d (1-1.25)

**Pts withdrawn from the list and not transplanted (n=5)**

Median nadir PT: 12% (9-12)  
Support for >3 organs

**Patients transplanted (n=4)**

At LT [ Median PT: 7.5% (5-13.5)  
Support for >3 organs

**Improved and alive  
N=15**

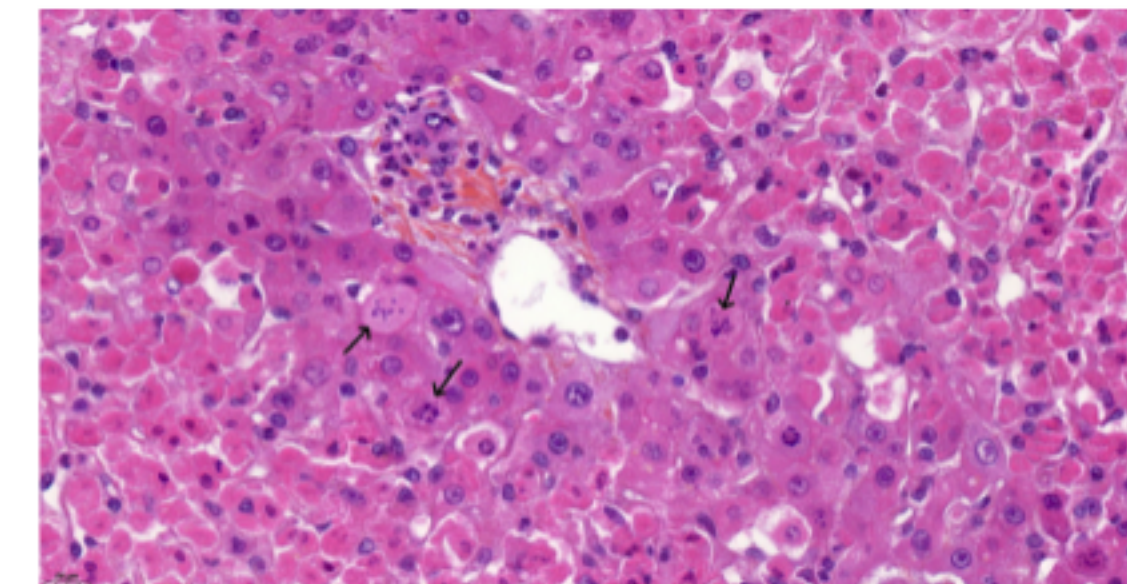
**Improved and alive  
N=5**

**Alive after LT at 1 yr  
n=3 (75%)**

**Died after LT (11 months)  
n=1**

**Overall survival with standard medical treatment  
n=20 (83%)**

**Native liver (n=4)**



Massive or sub-massive necrosis and "micronecrotic" appearance