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Prognostic factors in non-exertional heatstroke

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Abstract *Purpose:* To identify
the prognostic factors associated with
mortality in heat-related illness.
Methods: Multi-center observa-
tional cohort-study in 16 emergency
departments (ED) belonging to the
teaching hospital network of the Paris
area. The cohort comprised all
patients admitted to one of the EDs
during the August 2003 heat wave in
Paris and having a core tempera-
ture >38.5°C. Baseline clinical and
biological data in ED, patient's
course and 1-year survival rate were
recorded. Potential prognostic factors
associated with death were assessed
by Cox proportional-hazards analysis.
Results: A total of 1,456 patients
were included. Mean age was
79 ± 19 years. Critically ill condi-
tions were noted in 391 patients
(27%), but only 72 (5%) were
admitted into an intensive care unit.
The survival rate was 57% at 1 year
as compared to an expected 90%
(P < 0.001). Nine independent prog-
nostic factors were identified:
previous treatment with diuretics,
living in an institution, age >80 -
years, cardiac disease, cancer, core
temperature >40°C, systolic arterial

survival were assessed by the log–rank test. Univariate and multivariate Cox proportional-hazards models were used to determine the contribution of variables, expressed as hazard ratio and its 95% confidence interval (CI). To avoid overfitting, we used a conservative approach and included only the significant variables in the univariate analysis (P value of entry ≤ 0.10), except for some variables that were thought to be prognostic or had been demonstrated to be prognostic in previous studies. If the Pearson correlation coefficient between variables was 0.60 or more, only the variable judged to be clinically more relevant was entered. Continuous variables were transformed in dichotomous variables using receiver-operating characteristic (ROC) curves, the threshold being that which minimized the distance to the ideal point [17]. Inclusion in the final model was determined by a backward stepwise process. The discrimination of the model was assessed using the C statistic and its calibration using the Hosmer–Lemeshow statistic. To internally validate this model, we performed a ten-fold cross validation [18].

To develop a prognostic score, we assigned the prognostics factors identified by multivariate analysis using only variables available at admission and using weighted points proportional to the β regression coefficient values and rounded to the nearest integer. The population was divided into three categories: low, intermediate and high risk for death. The uncertainty surrounding the survival rate was evaluated using the standard bootstrap technique, and we calculated the mean and 95% CI of the survival rate at 1 year in the three risk groups [19].

To determine the naturally expected survival rate in this population, age and sex-specific mortality rate ratios were calculated with the use of life-expectancy values derived from life tables of the French national database (Institut National de la Statistique et des Etudes Economiques, Paris, France). We also performed a multiple backward logistic regression to assess variables associated with loss on follow-up.

All P values were two-tailed, and a P value < 0.05 was considered significant. Statistical analysis was performed using NCSS 2001 software (Statistical Solutions Ltd., Cork, Ireland).

Results

We included 1,461 patients, 5 of whom were excluded for missing important variables or young age. Thus, 1,456 patients constituted the study sample. Figure 1 shows the number of patients included at each date of the study period and the corresponding excess deaths and mean outside temperatures observed in France. The mean age was 79 ± 19 years; 689 patients (47%) had a core temperature >40°C, and 391 patients (27%) had critically ill
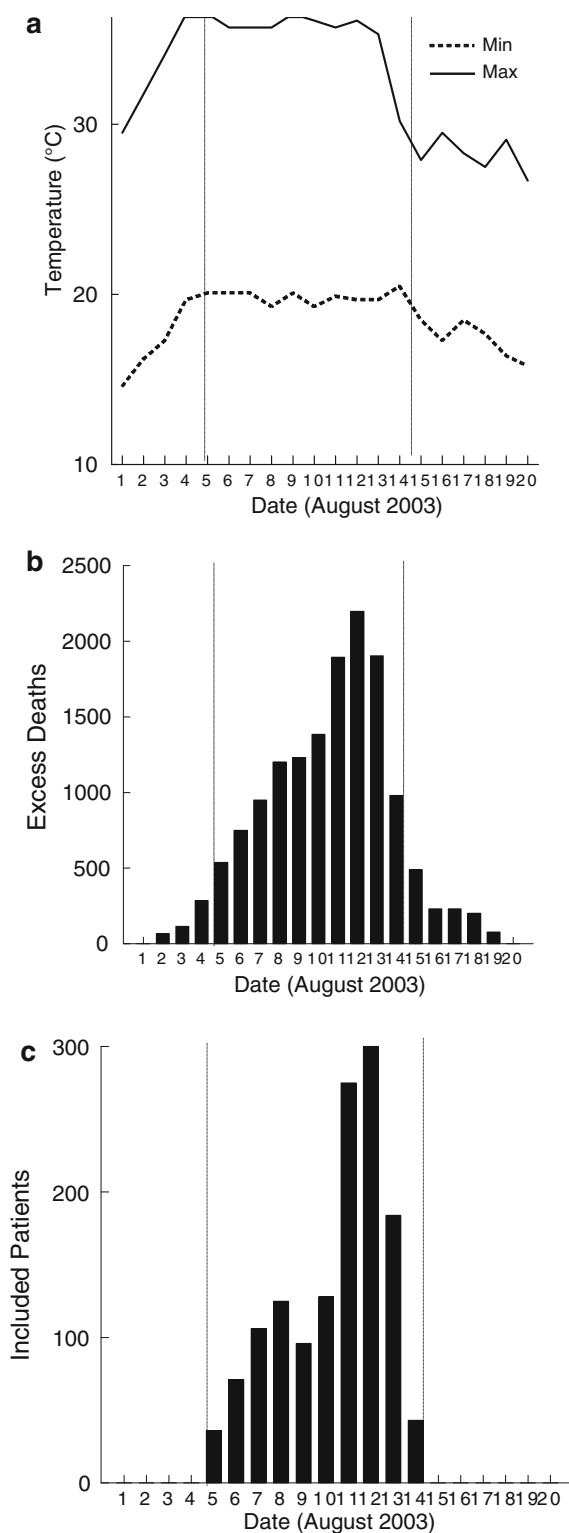

Fig. 1 Number of patients included (c) and comparison with the number of excess death (b) and mean maximum and minimum outside temperatures (a) recorded in France during August 2003. Data in a and b were those published by Fouillet et al. [8]. The *vertical dotted lines* indicate the inclusion period of the study
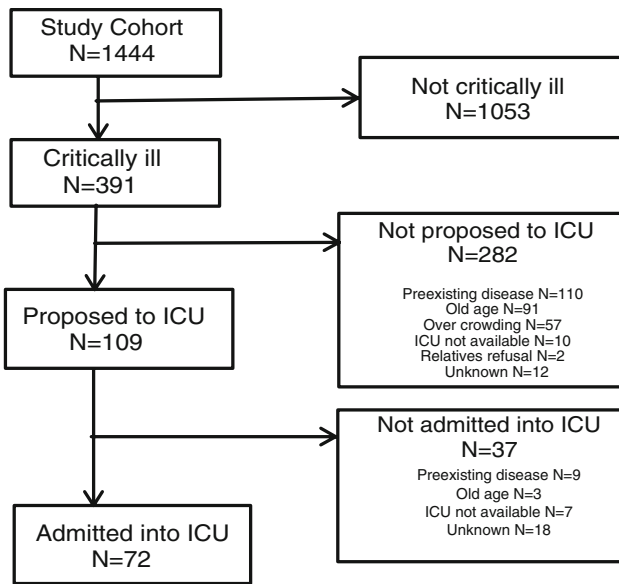
Fig. 2 Flow chart of the study according to critically ill conditions. Data were available for analysis by the expert panel in 1,444 patients rather than 1,456

conditions, but only 72 (5%) were admitted into an ICU (Fig. 2). According to the expert panel, the main diagnosis was heat-related illness in 88% of cases. Infection was diagnosed in 515 patients (36%), mainly pulmonary (45% of infected patients).

A cooling procedure was applied in 927 patients (64%), 15% during the prehospital phase and 59% in the ED. The methods of cooling were application of ice packs (66% of cooled patients) or wet sheets (84%), air ventilation (27%), spraying with aerosolized water (19%), putting the patient in an air-conditioned room (9%) and intravenous injection of cooled saline (5%). Antipyretic drugs (mainly acetaminophen) were administered in 932 patients (64%) and corticoids in 16 (1.1%).

During up to 1 year of follow-up, 160 patients (11%) entering the study were lost to follow-up. Four variables were significantly associated with a loss to follow-up: social precariousness (odds ratio 4.22, 95% CI 2.14–8.31, $P < 0.001$), lack of critically ill conditions (odds ratio 1.75, 95% CI 1.00–3.12, $P = 0.05$), a Glasgow coma score of 15 (odds ratio 1.92, 95% CI 1.22–3.03, $P = 0.005$) and lack of any pre-existing disease (odds ratio 1.75, 95% CI 1.47–3.33, $P < 0.001$).

The survival rate at 1 year was 57% (95% CI 54–59) and was significantly lower than that expected (90%, 95% CI 88–91) (Fig. 3). The hazard rate of the cohort rapidly decreased during the first 3 months (from 15.9 to 0.7%/week), then slowly decreased to 0.4 at 1 year and was close to that expected (0.2%/week) (Fig. 3).

The ADL scale at baseline was determined in 1,031 patients (71%). Among them, 41% died. It should be pointed out that 35% of the non-survivors were autonomy
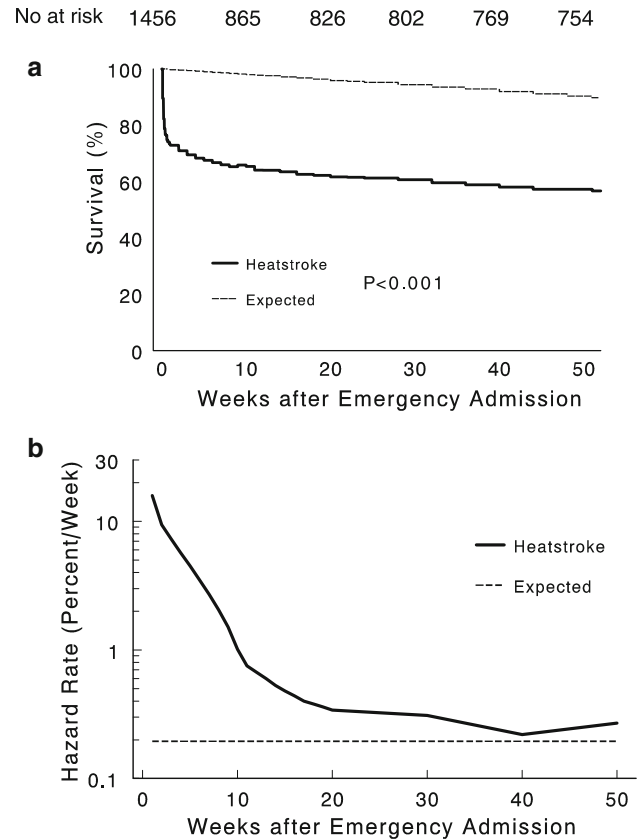
Fig. 3 Kaplan–Meier survival curves (**a**) and hazard rate (**b**) for the cohort and comparison with survival expected according to the life expectancy table in France ($n = 1,456$). The number of patients at risk at each time is shown above **a**

free (ADL = 6). The ADL scale at baseline and 1 year later was available in 607 surviving patients, and an impairment in ADL scale was noted in 18% (Fig. 4).

Table 1 shows that several variables were associated with a higher risk of death. Missing data from one or more variables restricted the analysis to 1,032 patients (71%). After exclusion of variables with a low prevalence or exhibiting multicolinearity, 26 variables were found to be of prognostic significance in the univariate analysis, and 11 variables maintained their prognostic significance after multivariate analysis (Table 1): age >80 years, cancer, cardiac disease, use of diuretics, living in an institution, transportation to hospital by an ambulance, white blood cell count >14,000/mm^3, a systolic arterial pressure <100 mmHg, a Glasgow coma scale <12, a core temperature >40°C, and the occurrence of pulmonary and/or bloodstream infection. Using the ten-fold cross validation technique, the area under the ROC curve [0.77 (95% CI 0.74–0.80)] was not significantly different from that of the model [0.78 (95% CI 0.76–0.81)].

To calculate a risk score, we used only variables available at the admission (Table 2). Missing data from one or more variables restricted the analysis to 1,198

Fig. 4 Analysis of morbidity in surviving patients ($n = 607$) using the activities daily living (*ADL*) scale. **a** Distribution of ADL (from 0, worse, to 6, best and autonomy free) at baseline and 1 year later. **b** Proportion of patients with unchanged, improved or impaired ADL scale
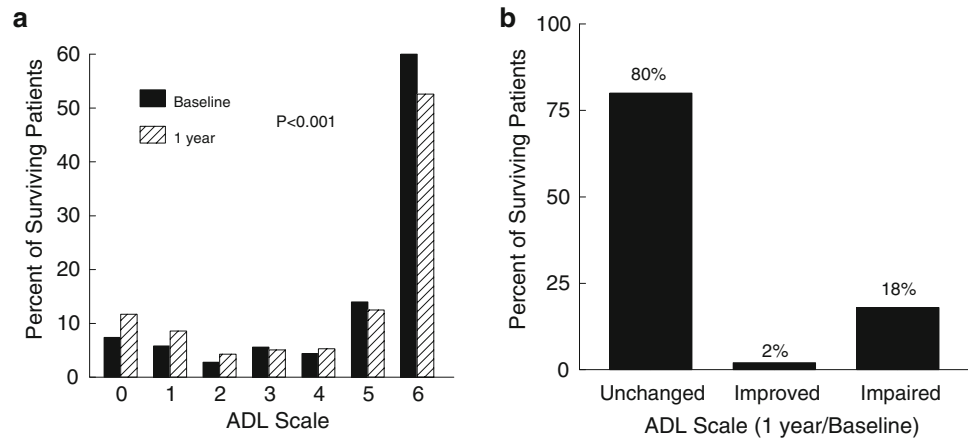
patients (82%). Survival estimates for each value of the score was used to define three groups: a low risk group (score: 0–6), an intermediate-risk group (score: 7–12) and a high-risk group (score: 13–22) (Fig. 5). The survival rates at 1 year for these three groups were 85% (95% CI 81–89), 61% (95% CI 57–65) and 18% (95% CI 13–23). The bootstrap analysis provided a survival rate at 1 year of 87% (95% CI 83–90), 63% (95% CI 59–66) and 19% (95% CI 14–24). In comparison, the expected survival at 1 year in these three groups was 92% (95% CI 89–94), 88% (95% CI 85–91) and 87% (95% CI 83–91).

Discussion

In this large cohort we observed a low survival rate, although entry to the study was on the basis of a definition of hyperthermia of core temperature >38.5°C, and a very low proportion of these patients was admitted into an ICU. We developed a risk score based on easily obtained variables that accurately predict mortality in these patients. In addition, the study has shown that 18% of surviving patients displayed impairment in their autonomy 1 year later.

The inclusion criteria used in our study require some comments. In contrast to previous studies [1, 9, 13], we included patients with a core temperature >38.5°C rather than >40°C or even 40.6°C. Our main argument was that considerable excess deaths were observed, even in patients without very high core temperatures, mainly because the population involved was aged and frail. The 1-year survival rate we observed was low (57%) and very close to that observed previously in patients with a higher core temperature [8]. Also because cooling was applied before reaching the hospital in at least 15% of these patients, the maximum temperature recorded may not reflect the maximum core temperature reached. Thus, our results suggest that the usual criteria for heatstroke (core temperature above 40°C and central nervous system

involvement)[1], which remain valid in exertional heatstroke occurring in young individuals, should no longer be retained during non-exertional heatstroke occurring during a heat wave, which represents a catastrophic event with major overcrowding of all health facilities. We also did not attempt to exclude infectious processes in our study for the following reasons: (1) many heatstroke were complicated by an infectious process, as previously reported [12, 13, 20]; (2) having an infectious process may facilitate the occurrence of a heatstroke. It should also be noted that since febrile patients represent less than 1–2% of patients usually seen in an ED [21], the proportion of patients having mainly an infectious process would have been limited in our study.

The survival rate was low, as previously reported [1, 9], but cannot be assessed without a comparison with expected survival rate since the population was old. This comparison shows that the hazard ratio (observed/expected) was close to 1 at 3 months after presentation (Fig. 3b), suggesting that most of the deleterious effects of heat-related illness can be observed during the first 3 months of the condition. Therefore, the number of excess deaths in France that was calculated during only August 2003 has probably been largely underestimated, as previously reported [22]. In surviving patients, heatstroke has been reported to be associated with important neuropsychological sequelae that may be important in elderly patients [7, 9]. Our study suggests that 18% of surviving patients experienced impairment in their autonomy (Fig. 5). Moreover, 35% of non-survivors were completely autonomous at baseline. This finding is at odds with the belief that almost all elderly patients who die during a heat wave are already severely disabled, indicating that more efforts should be attempted to provide appropriate prevention and care.

Our study demonstrates that the risk of death in patients attending EDs for heat-related illnesses during heat wave exposure could be predicted by the presence of 11 variables easily available at admission. These variables integrate an overview of parameters involved in heat-related illnesses

Table 1 Univariate and multivariate Cox proportional-hazards analysis predicting death

Prognostic factor	Prevalence no./total no. (%)	Univariate analysis		Multivariate analysis	
		Hazard ratio [95% CI]	P	Hazard ratio [95% CI]	P
Age >80 years	956/1,456 (66)	2.08 [1.71–2.52]	<0.001	1.45 [1.13–1.88]	0.004
Male sex	539/1,456 (37)	0.83 [0.71–0.99]	0.034		
Living in an institution	306/1,456 (21)	2.07 [1.74–2.45]	<0.001	1.35 [1.09–1.68]	0.006
Homeless or social precariousness	46/1,456 (3)	0.60 [0.34–1.06]	0.080		
Having a regular general practitioner	1,114/1,302 (86)	1.35 [1.03–1.75]	0.028		
Living alone	531/1,302 (41)	0.55 [0.46–0.66]	<0.001		
Having relatives	1,053/1,274 (83)	1.24 [098–1.58]	0.073		
Location before admission					
Medicalized location	246/1,452 (18)	2.16 [1.81–2.59]	0.073		
Non-medicalized location	1,206/1,452(82)	1	–		
Transportation to the hospital					
Medically manned ambulance	85/1,448 (6)	2.36 [1.82–3.08]	<0.001		
Non-medically manned ambulance	1,208/1,448 (84)	1	–	2.83 [1.32–6.06]	<0.001
Autonomous presentation	155/1,448 (10)	0.13 [0.07–0.24]	<0.001	1	
Pre-existing disease					
Neurological disease	377/1,421 (26)	1.49 [1.27–1.76]	<0.001		
Psychiatric disorder	319/1,421 (22)	1.28 [1.06–1.53]	0.022		
Dementia	191/1,421 (31)	1.44 [1.16–1.78]	0.001		
Hypertension	445/1,421 (31)	1.07 [0.90–1.28]	0.42		
Cardiac disease[a]	368/1,421 (25)	1.85 [1.56–2.19]	<0.001	1.40 [1.13–1.74]	0.002
Alcohol abuse	36/1,421 (2)	0.65 [0.35–1.21]	0.170		
Diabetes	157/1,421 (11)	1.12 [0.87–1.44]	0.366		
Cancer	108/1,421 (7)	1.59 [1.23–2.07]	<0.001	1.54[1.12–2.12]	0.007
Chronic respiratory disease	109/1,421 (7)	1.17 [0.88–1.57]	0.280		
Chronic renal insufficiency	25/1,421 (2)	1.42 [0.83–2.41]	0.196		
Chronic medication					
Diuretics	380/1,384 (27)	1.59 [1.34–1.89]	<0.001	1.25 [1.01–1.55]	0.037
CEI or AII I	260/1,384 (19)	1.35 [1.11–1.64]	0.003		
Beta-blockers	149/1,384 (11)	1.11 [0.86–1.43]	0.417		
Calcium inhibitors	180/1,384 (13)	1.14 [0.90–1.45]	0.262		
Nitrates	191/1,384 (14)	2.06 [1.69–2.53]	<0.001		
Inotropic drugs	112/1,384 (8)	1.39 [1.05–1.82]	0.020		
Antiarrhythmic drugs	113/1,384 (8)	1.36 [1.04–1.78]	0.027		
Anticoagulant or antiaggregants	445/1,384 (32)	1.44 [1.22–1.70]	<0.001		
Psychotropic drugs	633/1,384 (46)	1.43 [1.22–1.69]	<0.001		
Anti-inflammatory drugs	93/1,384 (7)	1.22 [0.90–1.65]	0.194		
Analgesic	211/1,384 (15)	1.35 [1.09–1.66]	0.006		
Statines	58/1,384 (4)	1.16 [0.79–1.71]	0.442		
Clinical signs					
Core temperature >40°C	689/1,456 (47)	2.21 [1.87–2.60]	<0.001	1.36 [1.11–1.67]	0.003
SAP <100 mmHg	355/1,398 (25)	3.72 [3.15–4.48]	<0.001	2.36 [1.92–2.92]	<0.001
Glasgow coma scale <12	328/1,319 (25)	5.18 [4.36–6.15]	<0.001	2.86 [2.30–3.55]	<0.001
Convulsions	50/1,431 (3)	2.82 [2.01–3.95]	<0.001		
Oxygen saturation <90%[b]	117/1117 (21)	2.73 [2.56–3.30]	<0.001		
Biological variables					
Leucocytes ≥14.0 G/l	850/1,230 (69)	1.88 [1.57–2.24]	<0.001	1.35 [1.10–1.65]	0.004
C reactive protein ≥6 mg/l	514/851 (60)	1.10 [0.89–1.37]	0.380		
Hypernatremia (>145 mmol/l)	213/1,263 (17)	1.39 [1.14–1.71]	0.001		
Hyponatremia (<135 mmol/l)	451/1,263 (36)	1.06 [0.89–1.27]	0.422		
Creatinine >120 μmol/l	546/1,248 (44)	1.71 [1.44–2.03]	<0.001		
Bicarbonates < 22 mmol/l	351/1,201 (29)	1.68 [1.41–2.01]	<0.001		
Arterial pH <7.38	128/458 (28)	1.99 [1.55–2.56]	<0.001		
Troponin Ic >0.15 ng/l	268/514 (52)	2.04 [1.58–2.62]	<0.001		
Infection					
Any infection	515/1,427 (36)	1.01 [0.85–1.20]	0.899		
Pulmonary or bloodstream	243/1,427 (47)	1.68 [1.39–2.03]	<0.001	1.50 [1.19–1.89]	0.001
Therapeutic cooling	927/1,456 (64)	1.72 [1.43–2.06]	<0.001		

SAP systolic arterial pressure; *CEI* converting enzyme inhibitor; *AII I* angiotensin II inhibitors

[a] Cardiac disease indicates coronary artery disease and/or heart failure

[b] Measured using pulse oximetry

Missing data from one or more variables restricted the multivariate analysis to 1,032 patients (71%)

Table 2 Multivariate Cox proportional-hazards analysis using only variables available at admission and scoring system

Prognostic factors	B regression coefficient [95% CI]	Odds ratio [95% CI]	Points
Chronic medication with diuretics	0.235 [0.035–0.434]	1.26 [1.04–1.54]	1
Living in an institution	0.317 [0.116–0.518]	1.37 [1.12–1.68]	1
Age >80 years	0.333 [0.101–0.564]	1.39 [1.11–1.76]	1
Cardiac disease[a]	0.336 [0.134–0.538]	1.40 [1.14–1.71]	1
Core temperature >40°C	0.361 [0.167–0.556]	1.44 [1.18–1.74]	2
Cancer	0.503 [0.207–0.799]	1.65 [1.23–2.22]	2
Systolic arterial pressure <100 mmHg	0.987 [0.796–1.178]	2.68 [2.22–3.25]	4
Glasgow coma scale <12	1.109 [0.908–1.309]	3.03 [2.48–3.70]	5
Transportation to hospital by ambulance[b]	1.285 [0.571–2.000]	3.62 [1.77–7.39]	5

CI confidence interval

[a] Cardiac disease indicates coronary artery disease and/or heart failure

[b] Includes transportation with physician-staffed ambulance (*SAMU*) and paramedics-staffed ambulance

Missing data from one or more variables restricted the analysis to 1,198 patients (82%)
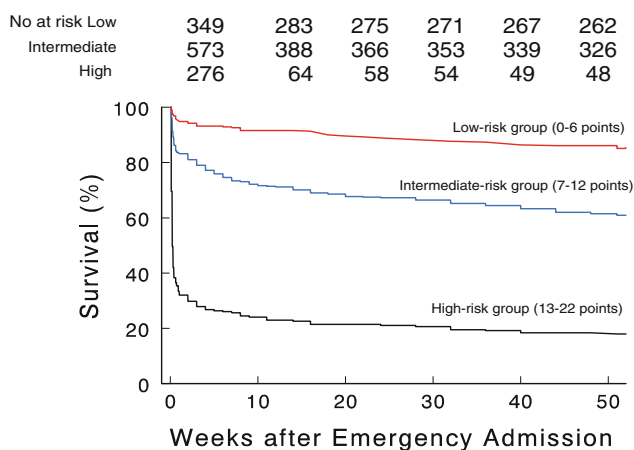

Fig. 5 Kaplan–Meier survival curves according to the prognostic classification. Because data for some variables were missing for some patients, the prognostic classification was based on a total of 1,181 patients rather than 1,456. Risk categories were determined by adding up the points for each prognostic factor (see Table 2). The number of patients at risk at each time is shown above the figure

psychotropic drugs have been constantly reported as a risk factor for heatstroke exposure [2, 12], but appear to not be very important when heatstroke occurs. This was also the case for social precariousness.

The health consequences of a heat wave may be catastrophic [2–4, 8–13]. For this reason, considerable efforts have been made to identify climatic factors that predict the occurrence of heat waves, individual factors that favor the occurrence of heatstroke during a heat wave, or even factors that may alert the ED to prehospital heat-related excess mortality [24]. Our risk score provides a useful tool for the emergency team, allowing better allocation of therapeutic options, including access to the ICU. Although many of the patients in this study were probably not good candidates for admission to the ICU either because of old age and/or comorbidities or reduced autonomy, we think that the very low proportion of patients finally admitted (5%) indicates considerable overwhelming of health capacities as well as an underestimation of the severity of the disease, mainly in patients without a very high core temperature. It is noteworthy that there is convincing evidence in the literature that age, by itself, is not an appropriate means of selection of patients admitted to the ICU [25].

This study has several limitations. First, we have probably overestimated the expected survival in our cohort since the life expectancy tables used refer to the whole French population, and it is likely that patients presenting at an ED have a lower survival rate because of more frequent associated diseases. This overestimation is probably of minor magnitude since the survival rate in the low-risk group was not markedly different from that expected. Second, some important prognostic variables may have been missed because they were recorded in only a few patients (arterial pH, troponin) or because of the lack of power in the case of low prevalence. We also excluded variables not available at admission in our risk score, although some of them provided useful prognostic information (leucocytes, infectious complication). Third, the multivariate model identifies an association between

severity: some of them indicate a greater susceptibility to heatstroke (age, pre-existing disease such as cancer, cardiac disease or chronic medication with diuretics), other variables more specifically reflect the severity of heatstroke's consequences itself (core temperature, systolic arterial pressure, consciousness and leucocyte count) [12, 23], both (transportation to hospital by ambulance), or finally heatstroke complications (pulmonary or bloodstream infection). Our risk score (Table 2) accurately classified patients into subgroups at low, intermediate and high risk for death (Fig. 5). The survival rate of the the low-risk group was close to that expected using the life expectancy tables. The present study enables a clearer understanding of prognostic factors for heatstroke during a heat wave and those that favored death when heatstroke occurred. For example, psychiatric disorders and/or use of

prognostic factors and death and does not indicate causality. Nevertheless, there is strong suspicion of a causal link among the identified prognostic factors because they refer either to the severity of heatstroke (core temperature, systolic arterial pressure, consciousness), to a greater susceptibility to heatstroke (age, preexisting disease) or to a complication of heatstroke (severe infection). Finally, the multivariate model did not identify cooling as an independent protective factor (see Table 1), even when this variable was forced into the model (data not shown). This could be explained either by a severity bias (the most severe patients having a higher probability of death and a higher probability to receive cooling procedures) or by the discrepancy between time of measurement of temperature and time of cooling since some patients received pre-hospital cooling.

In conclusion, in a large cohort of patients with non-exertional heat-related illness, we observed a low 1-year survival rate (56%), although our inclusion criterion for considering heatstroke was a body temperature as low as 38.5°C. This low survival rate should be compared with the relatively low proportion of cooled patients (64%), the high proportion of pulmonary and/or bloodstream infection (35%) and the low proportion of patients admitted to the ICU (5%). We developed a risk score based on easily obtained variables that accurately predict mortality in these patients. These findings may be useful to clinicians in order to allocate therapeutic priorities during a heat wave catastrophic event, which markedly enhances the usual overcrowding of ED. The classical definition of heatstroke (core temperature >40°C) should probably be modified (core temperature >38.5°C) during a heat wave.

Appendix

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