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Severe Imported Falciparum Malaria: A Cohort Study in 400 Critically Ill Adults

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Abstract

**Background:** Large studies on severe imported malaria in non-endemic industrialized countries are lacking. We sought to describe the clinical spectrum of severe imported malaria in French adults and to identify risk factors for mortality at admission to the intensive care unit.

**Methodology and Principal Findings:** Retrospective review of severe *Plasmodium falciparum* malaria episodes according to the 2000 World Health Organization definition and requiring admission to the intensive care unit. Data were collected from medical charts using standardised case-report forms, in 45 French intensive care units in 2000–2006. Risk factors for in-hospital mortality were identified by univariate and multivariate analyses. Data from 400 adults admitted to the intensive care unit were analysed, representing the largest series of severe imported malaria to date. Median age was 45 years; 60% of patients were white, 96% acquired the disease in sub-Saharan Africa, and 65% had not taken antimalarial chemoprophylaxis. Curative quinine treatment was used in 97% of patients. Intensive care unit mortality was 10.5% (42 deaths). By multivariate analysis, three variables at intensive care unit admission were independently associated with hospital death: older age (per 10-year increment, odds ratio [OR], 1.72; 95% confidence interval [95%CI], 1.28–2.32; \( P = 0.0004 \)), Glasgow Coma Scale score (per 1-point decrease, OR, 1.32; 95%CI, 1.20–1.45; \( P < 0.0001 \)), and higher parasitemia (per 5% increment, OR, 1.41; 95%CI, 1.22–1.62; \( P < 0.0001 \)).

**Conclusions and Significance:** In a large population of adults treated in a non-endemic industrialized country, severe malaria still carried a high mortality rate. Our data, including predictors of death, can probably be generalized to other non-endemic countries where high-quality healthcare is available.

Introduction

*Plasmodium falciparum* malaria remains a major public health problem in endemic areas, with more than 1,000,000 deaths each year. About 12,000 cases of imported malaria are reported annually in Europe [1] and about 1300 in the United States [2]. Among non-endemic countries, France has the highest number of cases, about 5000 per year, of which 20 to 30 are fatal [3]; the
Severe imported malaria still carries a high mortality rate, which is estimated at 10% to 15%, although large studies are lacking [3]. One of the objectives of the World Health Organization (WHO) program for malaria control in Europe is to identify risk factors for death that can be used to optimize treatment decisions. In 2003, we reported several risk factors identified in 188 patients admitted to a single French intensive care unit (ICU) in 1988–1999 [5]. Although this study was the largest on managing severe malaria in a non-endemic industrialized country, it was conducted in a single center, over a long period, and used the 1990 WHO definition of severe malaria [6]. The WHO issued a new definition in 2000 [7]. Moreover, new treatment strategies for severe sepsis have been introduced over the last decade.

The objectives of this study were to gather multicenter data about severe imported malaria managed in the ICU in recent years, and to identify risk factors for mortality present at ICU admission.

Methods

Ethics Statement

Our study was approved by the Ethics Committee of the French Society for Critical Care Medicine (approval #07-211). Due to the retrospective design of the study, we did not obtain informed consent from the included patients. Nevertheless, all the data collected retrospectively were anonymized in a standardized case-report form and in the database.

Study sites and population

The study was performed in the 45 adult ICUs in France that constitute the SIMA Study Group of 30 civilian university hospitals, three military teaching hospitals, and 12 regional nonteaching hospitals. Consecutive adults admitted to the 45 ICUs with a diagnosis of severe falciparum malaria between January 2000 and October 2006 were included and data were collected retrospectively (in 2006–2007) from the medical charts using standardized case-report forms.

Definitions

According to the 2000 WHO definition [7], severe imported malaria was defined in this study as the combination of, (i) asexual P. falciparum forms in blood or a positive result of the P. falciparum histidine-rich protein 2 antigen-based rapid test, and (ii) one or more severity criteria (Table 1) at admission or within the first 2 days, and (iii) requirement of ICU admission (at the discretion of the ICU physicians). The 2000 WHO definition of severe malaria [7] was modified in part according to the SEAQUAMAT group [8]. More specifically, respiratory distress criteria were defined as stated in Table 1. Moreover, and to better characterize lung injury, we also defined respiratory failure as follows: in spontaneously breathing patients, PaO2 <60 mmHg on room air or need for supplemental oxygen and/or respiratory rate >32/ min; and in patients receiving ventilatory assistance, PaO2/FiO2 ratio <200 mmHg.

Nonimmune patients were defined as Caucasians who traveled occasionally to endemic areas [5].

Community-acquired co-infection was defined as any infection diagnosed within the first 2 days after hospital admission. Infections occurring later were considered nosocomial. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) were defined according to Bernard et al. [9].

Management

Treatment, particularly the management of organ dysfunctions (including levels for blood products transfusions), was at the discretion of the ICU physicians. During the study period, recent and detailed French guidelines for the management of severe

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**Table 1.** Clinical and biological criteria for severe malaria according to the 2000 World Health Organization definition with modifications (see * and †).

| Clinical criteria | Impaired consciousness: Glasgow Coma Scale score <11* |
|-------------------|--------------------------------------------------|
| Respiratory distress: requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO2 <60 mm Hg (if FiO2 ≥0.21) †, and/or respiratory rate >32/min* |
| Multiple convulsions |
| Circulatory collapse: systolic blood pressure <80 mm Hg despite adequate volume repletion |
| Abnormal bleeding |
| Jaundice: clinical jaundice or bilirubin >50 μmol/L |
| Macroscopic hemoglobinuria: if unequivocally related to acute malaria (patients with blackwater fever were not included) |
| Laboratory criteria |
| Severe anemia: hemoglobin <5 g/dL |
| Hypoglycemia: blood glucose <2.2 mmol/L |
| Acidemia (pH<7.35) or acidosis (serum bicarbonate <15 mmol/L) |
| Hyperlactatemia: arterial lactate >5 mmol/L |
| Hyperparasitemia ≥4% |
| Renal impairment: serum creatinine >265 μmol/L or blood urea nitrogen >17 mmol/L* |

*Coma scale criteria of 11 instead of 9; respiratory rate >32/minute and blood urea nitrogen >17 mmol/L are modifications according to the SEAQUAMAT group [8]. †The requirement for noninvasive and/or endotracheal mechanical ventilation or spontaneous breathing with PaO2 <60 mm Hg (if FiO2 ≥0.21) was used specifically for this study.

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falciparum malaria were available [10]. These guidelines strongly recommended a quinine loading dose but did not recommend exchange transfusion.

Blood culture for microbiology and chest X-ray were performed routinely at ICU admission. Neuroimaging, electroencephalogram and hemodynamic investigations were performed if deemed necessary by the attending physician.

Data collection
We recorded demographic data; previous medical history; country of malaria acquisition; chemoprophylaxis; clinical, laboratory, and imaging findings; and treatments and vital status at ICU and hospital discharge. Severity at ICU admission was assessed by computing the Glasgow Coma Scale (GCS) score [11], Simplified Acute Physiology Score II (SAPS II) [12], and Sequential Organ Failure Assessment (SOFA) score [13]. In each ICU, one intensivist completed a standardized case-report form for each patient. All case-report forms were reviewed by one of us (FB) for identification and resolution of inconsistencies.

Statistical analysis
A descriptive analysis was performed on the overall sample. Categorical variables were described with numbers and percentages and continuous variables with mean and SD, or with median and interquartile range [IQR] for non-normally distributed variables. Survivors and nonsurvivors were compared using the chi-square test for categorical variables and the Student’s t-test or Wilcoxon rank-sum test, as appropriate, for continuous variables.

To identify risk factors for mortality, we constructed logistic regression models using a combination of multiple imputations and bootstrapping to select prognostic variables and to handle missing data [14]. Potential risk factors were as follows: *worst value during the 24 hours after ICU admission; sex, ethnic origin, co-morbidities, pulmonary failure*, shock*, age, time from symptom onset to ICU admission, GCS score*, plasma bicarbonate*, hemoglobin*, leukocytes*, platelets*, prothrombin time*, plasma creatinine*, highest blood glucose*, lowest blood glucose*, total serum bilirubin*, ALAT*, and parasitemia*. From the initial data set, we constructed 1000 bootstrap data sets and performed automatic stepwise logistic regression in each, selecting variables associated with mortality with *P < 20% by univariate analysis. Then, variables were selected for the second step if they were associated with mortality with *P values < 20% in at least 20% of the 1000 models. We implemented multiple imputation of missing data, which yielded five data sets. We then constructed 1000 bootstrap data sets for each imputed data set (i.e., 5000 data sets) and performed automatic stepwise logistic regression in each. Variables present in at least 60% of the 5000 models were selected for the final model. In the last step, we used the mean of the coefficient estimations obtained in each of the five imputed data sets. SAS 9.1 software (SAS Inc, Cary, NC) was used for all statistical analyses.

Results
During the study period, 400 patients admitted to the ICU for severe falciparum malaria, were included. The median number of patients per center was 7 (IQR, 5–10; range, 2 to 35).

General characteristics of the 400 patients
These characteristics are reported according to survival status in Table 2. Falciparum malaria was acquired in sub-Saharan Africa in 95.5% of the 366 patients for whom this information was available. Median stay duration in the endemic area was 1.0 month (IQR, 0.5–2.0). Of the 34.7% of patients who reported taking anti-malarial chemoprophylaxis, only 45.5% reported good adherence. Conditions associated with immune deficiency were noted in 7.3% of patients. One or more co-morbidities were present in 14.3% of patients. Five patients were pregnant.

Baseline patient characteristics and antimalarial therapy at ICU admission
The main clinical and laboratory characteristics and the pattern of WHO severity criteria during the first 24 hours in the ICU in survivors and nonsurvivors are reported in Tables 3 and 4, respectively.

Overall, median parasitemia at ICU admission was 7.0% (IQR, 2.7–15.0%). *P. falciparum* was identified in thin blood films in 84.7% of patients and/or in thick blood films in 50.7% and/or by antigen detection in 11.5%.

Intravenous quinine was used in 391 (97.8%) patients and other antimalarials in 9 patients. A quinine loading dose was used in 244 (61%) patients. The mean loading dose was 1072±359 mg, consistent with the mean body weight (72.7±14.5 kg) and French

| Parameter                              | Survivors n = 358 | Nonsurvivors n = 42 | P value* |
|----------------------------------------|-------------------|---------------------|----------|
| Mean age (±SD), years                  | 42.8±15.0         | 55.6±14.2           | <0.0001  |
| Male, %                                | 68.3              | 83.3                | 0.04     |
| White, %                               | 57.7              | 79.5                | 0.01     |
| Black, %                               | 36.0              | 12.8                |          |
| Other, %                               | 6.3               | 7.7                 |          |
| Previous malaria episodes, %           | 23.4              | 17.1                | 0.36     |
| Antimalarial chemoprophylaxis, %       | 34.8              | 34.1                | 0.94     |
| Nonimmune patients, %                  | 43.8              | 59.5                | 0.05     |
| At least one co-morbidity, %           | 13.1              | 23.8                | 0.06     |
| Immune deficiency, %                   | 7.8               | 2.6                 | 0.34     |
| Mean time from symptom onset to ICU admission (±SD), days | 5.4±5.1 | 6.2±4.6 | 0.14 |

ICU, intensive care unit; SD, standard deviation.
* according to univariate analysis.
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### Table 3. Baseline characteristics at intensive care unit admission in the 400 patients by survival status.

| Parameter                                             | Survivors n = 358 | Nonsurvivors n = 42 | P value* |
|-------------------------------------------------------|-------------------|---------------------|----------|
| SAPS II, mean±SD                                       | 30.2±15.6         | 70.6±26.3           | <0.0001  |
| SOFA score, mean±SD                                   | 7.7±3.8           | 15.4±5.2            | <0.0001  |
| Glasgow Coma Scale score, median [IQR]                | 15.0 [12.0–15.0]  | 9.0 [3.0–14.0]      | <0.0001  |
| Respiratory failure %                                  | 13.4%             | 45.2%               | <0.0001  |
| Highest temperature in °C, mean±SD                    | 39.0±1.1          | 38.7±1.1            | 0.08     |
| Arterial pH, mean±SD                                   | 7.41±0.1          | 7.19±0.2            | <0.0001  |
| Serum bicarbonates in mmol/L, mean±SD                 | 21.7±4.7          | 15.7±7.2            | <0.0001  |
| Arterial lactate in mmol/L, median [IQR]              | 2.4 [1.6–4.0]     | 8.4 [4.5–16.0]      | <0.0001  |
| Hemoglobin in g/dL, mean±SD                           | 10.3±2.6          | 9.2±2.9             | 0.01     |
| WBC, 10^3/mm³, median [IQR]                           | 6.4 [4.7–9.6]     | 9.7 [5.9–17.9]      | 0.004    |
| Platelet count, 10^9/mm³, median [IQR]                | 35.0 [19.0–57.0]  | 19.0 [13.0–29.0]    | <0.0001  |
| Plasma prothrombin time in %, mean±SD                 | 72.6±16.8         | 53.4±26.8           | <0.0001  |
| Serum creatinine in µmol/L, median [IQR]              | 117.0 [87.0–228.0]| 203.0 [156.0–302.0]| <0.0001  |
| Lowest serum glucose in mmol/L, mean±SD               | 5.4±2.1           | 4.7±2.4             | 0.03     |
| Serum lactate dehydrogenase in IU, median [IQR]       | 96.0 [600.0–1428.0]| 2239.5 [1121.0–4128.0]| <0.0001  |
| Serum C-reactive protein in mg/L, mean±SD             | 165.2±86.8        | 198.8±93.7          | 0.06     |

ICU, intensive care unit; SD, standard deviation; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count; ALAT, alanine aminotransferase; IU, international units.

*according to univariate analysis.

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### Table 4. Severity criteria in the 400 patients at intensive care unit admission, according to outcome.

| Severity criteria                          | Survivors n = 358 | Nonsurvivors n = 42 | P value* |
|-------------------------------------------|-------------------|---------------------|----------|
| Impaired consciousness, n (%)             | 77 (21.5)         | 26 (62.0)           | <0.0001  |
| Respiratory distress, n (%)               | 72 (20.1)         | 29 (69.1)           | <0.0001  |
| Multiple convulsions, n (%)               | 22 (6.2)          | 5 (11.9)            | 0.1849   |
| Shock, n (%)                              | 69 (19.3)         | 26 (61.9)           | <0.0001  |
| Abnormal bleeding, n (%)                  | 7 (2.0)           | 3 (7.1)             | 0.0766   |
| Jaundice, n (%)                           | 178 (49.7)        | 30 (71.4)           | 0.0077   |
| Hemoglobinuria, n (%)                     | 20 (5.6)          | 2 (4.8)             | 1.0000   |
| Severe anemia, n (%)                      | 10 (2.8)          | 4 (9.5)             | 0.0453   |
| Hypoglycemia, n (%)                       | 5 (1.4)           | 8 (19.1)            | <0.0001  |
| Acidosis, n (%)                           | 43 (12.0)         | 27 (64.3)           | <0.0001  |
| Hyperlactatemia, n (%)                    | 37 (10.3)         | 26 (61.9)           | <0.0001  |
| Parasitemia > 4%, n (%)                   | 223 (62.3)        | 34 (81.0)           | 0.0170   |
| Renal impairment, n (%)                   | 111 (31.0)        | 26 (61.9)           | <0.0001  |
| Mean number of severity criteria during the first 24 hours in the ICU (± SD) | 2.4±1.6 | 5.9±2.4 | <0.0001 |

WHO, World Health Organization; ICU, intensive care unit.

*according to univariate analysis.

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Complications of malaria and management

In 97 (24.3%) patients, at least one WHO defining criterion that was absent during the first 24 hours developed over the next 48 hours: impaired consciousness (n = 20), respiratory distress (n = 45), multiple convulsions (n = 6), shock (n = 26), abnormal bleeding (n = 6), jaundice (n = 12), hemoglobinuria (n = 2), severe anemia (n = 6), hypoglycemia (n = 5), acidosis (n = 10), hyperlactatemia (n = 7), hyperparasitemia (n = 4), and renal function impairment (n = 23).

Consciousness was impaired in 123 patients (103 at admission), for a mean duration of 2 days (IQR, 1–6; range, 1–67). Convulsions occurred in 33 patients, of whom 21 needed anticonvulsant therapy. Focal neurological abnormalities were present in 22 patients. Cerebral computed tomography (CT) and/or magnetic resonance imaging (MRI) were performed in 76 and 15 patients, respectively, and the findings were abnormal in 25 patients. At ICU discharge, 24 patients had at least one residual neurological abnormality: mental status abnormalities (n = 12), persistent focal deficits (n = 6), critical illness polyneuropathy (n = 6), epilepsy (n = 2), and other abnormalities (n = 7).

On the first day, fluid resuscitation was given to 247 (61.7%) patients, including 25 (25/358, 7.0%) survivors and 5 (5/42, 90.5%) nonsurvivors (P = 0.0076). The main co-infection sites and microorganisms are detailed in the Table 5.

Endotracheal mechanical ventilation was required in 116 (116/395, 29.4%) patients, for a median duration of 6 days (IQR, 3–14; range, 1–201). In addition, 32 patients received noninvasive ventilation, which failed in 16 patients, who then received endotracheal mechanical ventilation. Thus, mechanical ventilation was used in 132 patients, of whom 90 survived and 42 died. Nonhemolytic pulmonary edema was present in 76 (57.5%) of the 132 ventilated patients; among them, 30 had ARDS and 16 had ALI. The 56 other patients received ventilatory assistance essentially because of unarousable coma.

During the ICU stay, 81 patients required renal replacement therapy (intermittent hemodialysis, n = 64; and/or continuous veno-venous hemodiafiltration, n = 49).

Abnormal bleeding occurred in 23 patients. Blood transfusions were required in 114 patients, platelets in 63, and fresh plasma in 24. Overall, 104 blood-product units were transfused (538 blood, 177 platelets, and 130 fresh plasma units).

**Outcomes and factors predicting death**

The overall hospital mortality rate was 10.5% (95% confidence interval [95%CI], 7.5%–13.5%), because all 42 deaths occurred in the ICU. The main characteristics of the nonsurvivors and causes of death are shown in Table S1. Death occurred within the first ICU week in 32 (76.2%) patients. Median ICU stay duration in the 42 patients who died was 3.5 days (IQR, 2–7; range, 1–196). Median ICU and hospital stay durations in survivors were 5 days (IQR, 3–8; range, 1–186) and 10 days (IQR, 7–17; range, 1–189), respectively.

By multivariable analysis, three variables present within 24 hours after ICU admission were significantly associated with death in the ICU: older age, lower Glasgow Coma Scale score, and higher parasitemia (Table 6).

**Discussion**

In 400 adults with severe imported malaria, ICU mortality was 10.5%. Three variables present at ICU admission independently predicted death: older age, coma, and higher parasitemia.

Table 5. Data on the 96 first episodes of co-infection in the 400 adults with severe imported malaria.

| Parameter | Community-acquired infections n = 30 | Nosocomial infections n = 66 |
|-----------|-----------------------------------|-----------------------------|
| **Pneumonia** | | |
| Microorganisms (number of episodes) | 13 episodes | 48 episodes |
| Streptococcus pneumoniae (3), MS Staphylococcus aureus (3), Gram- cocc (negative culture) (1), Escherichia coli (1), Haemophilus influenzae (1), Klebsiella pneumoniae (1), Enterobacter cloacae (1), Acinetobacter baumannii (1), Pseudomonas aeruginosa (1), Not documented (2) | MS S. aureus (11), Streptococcus sp (7), S. pneumoniae (3), MR S. aureus (1), H. influenzae (9), E. coli (4), K. pneumoniae (1), Enterobacter aerogenes (3), E. cloacae (2), A. baumannii (3), P. aeruginosa (5), Burkholderia cepacia (1), Legionella pneumophila (1), Citrobacter koseri (1), Not documented (6) |
| **Bacteremia** | 10 episodes | 8 episodes |
| Microorganisms (number of episodes) | E. coli (3), P. aeruginosa (1), Alcaligenes xylosoxidans (1), Clostridium sp (1), K. pneumoniae (1), Salmonella typhi (1), Campylobacter jejuni (1), Candida albicans (1) | E. coli (4), MS S. aureus (1), Staphylococcus epidermidis (1), Klebsiella oxytoca (1), S. typhi (1) |
| **Urinary tract infection** | 3 episodes | 9 episodes |
| Microorganisms (number of episodes) | E. coli (2), Proteus sp (1) | E. coli (3), K. pneumoniae (3), Enterococcus sp (2) |
| **Other sites of infection** | | |
| Microorganisms (number of episodes) | Abdominal infection (3), Skin and soft tissue (1) | Catheter infection (3), Sinusitis (2) |

MS, methicillin-susceptible; MR, methicillin-resistant. doi:10.1371/journal.pone.0013236.t005

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Severe Imported Malaria

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Pneumonia

Microorganisms (number of episodes)

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MS, methicillin-susceptible; MR, methicillin-resistant. doi:10.1371/journal.pone.0013236.t005
Table 6. Independent predictors of death at intensive care unit admission in the 400 patients.

|                      | N   | OR (95%CI) | P value |
|----------------------|-----|------------|---------|
| Age (per 10-year increment) | 400 | 1.72 [1.28–2.32] | 0.0004  |
| Glasgow Coma Scale score (per 1-point increment) | 400 | 1.32 [1.20–1.45] | <0.0001 |
| Parasitemia (per 5% increment) | 400 | 1.41 [1.22–1.62] | <0.0001 |

R² of the model: 0.90.
OR, odds ratio; 95%CI, 95% confidence interval.
doi:10.1371/journal.pone.0013236.t006

To the best of our knowledge, this is the largest study of severe imported falciparum malaria in adults managed in a nonendemic country with high-level intensive-care facilities. It provides useful insights on disease outcomes and variables contributing to mortality, at least in France. These results should prove useful to clinicians managing severe malaria patients in the ICU, as well as to epidemiologists and public health practitioners studying potential risk factors for mortality in severe imported malaria. They may help to provide recommendations for intensivists, especially in countries where imported malaria is uncommon.

Whether our results can be generalized to other nonendemic countries deserves discussion. The few recent studies on severe imported malaria cannot be compared directly, for multiple reasons. Nevertheless, a large number of factors can influence the mortality of severe imported malaria. They may help to provide recommendations for intensivists, especially in countries where imported malaria is uncommon.

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cases of falciparum malaria, of which 72 were severe and 6 were fatal, the odds of having severe falciparum malaria were 12 times higher in patients with parasitemia ≥2% than in those with parasitemia <2% [15]. Further studies are needed to clarify the relevance of both parasitemia and plasma P. falciparum HRP2 as predictors of death in adults with severe imported malaria.

Although an earlier study showed that ethnic origin was an independent risk factor for severe malaria [15], ethnic origin did not independently predict death in our study. We cannot rule out a weak association of ethnic origin with mortality in patients who already have severe malaria, and our sample size may have been too small to detect a statistically significant effect.

Finally, to better assess the relevance of co-infections, we included “at least one infection” in the multivariable model. This parameter was not significant, suggesting that it did not independently predict death. In our setting, co-infections seem associated with severity rather than independently responsible for increased severity.

Our study has strong points compared to the main recent studies of severe imported malaria [5,15]. The patient population is considerably larger and comes from 43 different centers, which increases the general validity of our findings. Furthermore, our study covers a recent period and therefore reflects the impact of the many recent advances in the management of severe sepsis [23,24]. Finally, nearly all the patients received quinine therapy and, therefore, our results were not confounded by differences in the antimalarial drugs used. One limitation of our study is the retrospective design. However, the database was established by collecting information on consecutive patients using standardized data-collection forms. To obtain an adequate recruitment rate, we had to select adult ICUs experienced in the management of severe malaria, and consequently only 45 ICUs participated in the study. Some data were missing from the database. Nevertheless, this point was carefully taken into account and corrected by the statistical methodology using both multiple imputation and bootstrapping [14].

Our findings suggest several targets for improving the management of severe imported malaria. First, inappropriate chemoprophylaxis was common among both survivors and nonsurvivors. Efforts to improve adherence to chemoprophylaxis regimens are clearly needed. Second, we identified several independent predictors of death. A more standardized and aggressive treatment approach to patients with these predictors (and in particular immediately upon the onset of neurological impairment) might decrease the mortality rate. Third, we used quinine in nearly all our patients. A large study of adults with severe malaria conducted recently in Asia found that artesunate was associated with lower mortality rates and better tolerance, compared to quinine [8]. Thus, it can be hoped that the introduction of intravenous artesunate in nonendemic areas will improve survival rates in patients with severe imported malaria [25]. Unfortunately, intravenous artesunate is not yet available in France or other European countries. The only data on artesunate therapy for severe imported falciparum malaria come from a letter about 9 Norwegian patients, all of whom achieved a full recovery [26], and from the 2008 report of the Centers for Disease Control about 9 Norwegian patients, all of whom achieved a full recovery [26].

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Hospita Yves Le Foll, Saint Brieuc: A. Courte and G. Guivarch (ICU), L. Guenennec (Parasitology).  
Hospita Begin, Saint Mande: N. Libert and JM. Rousseau (ICU), C. Rapp, JE. Pilo and JD. Cavallo (Parasitology).  
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Hospita Lapeyronie, Montpellier: K. Klouche and P. Beraud (ICU), JP. Cristiol and JP. Dedet (Parasitology).  
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**Author Contributions**

Conceived and designed the experiments: FB FT MW. Performed the experiments: FB BM JPM EP CC FS EA YG AM HH JLT EF LN MN MW. Analyzed the data: FB FT BM JPM EP CC FS EA YG AM HH JLT EF LN CR RD JLB MW. Wrote the paper: FB FT BM JPM EP CC FS EA YG AM HH JLT EF LN CR RD JLB MW.

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