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Severe *Plasmodium falciparum* malaria in the intensive care unit: a 6-year experience in Milano, Italy

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Summary

Background: Severe imported *Plasmodium falciparum* malaria is a potentially life-threatening disease with a reported mortality rate of 4-10% when patients are admitted to the Intensive Care Unit.

Methods: To retrospectively review the clinical aspects, the value of severity predictive scores and the management of patients with severe *P. falciparum* malaria admitted to an ICU in Milano, Italy between January 2010 and December 2015

Results : Twelve patients were included: seven were male and five female with a median age of 43 years. All were initially treated with intravenous quinine. Median parasitemia upon admission was 14.5% (range 1-20%). At the time of ICU admission, 3 patients (25 %) had 5 or more World Health Organization criteria for severe malaria while another 6 of them developed one or more of the latter during their stay in ICU. Five required mechanical ventilation because of respiratory failure due to ARDS. Four patients required renal replacement therapy. Three patients underwent blood exchange transfusion. All patients survived

Conclusions: Our retrospective evaluation of adults patients admitted to the ICU with severe imported *P. falciparum* malaria demonstrated a favourable outcome. Severity predictive scores currently in use probably overestimate the risk of malaria mortality in patients treated in health care systems of high income countries.

1. Introduction

Although declining worldwide, malaria was responsible in 2015 of 214 million clinically apparent cases and 438.000 associated deaths. A disproportionate majority (90%) of cases still occurred in sub-Saharan Africa with death (67%) observed especially among under-five years children [1]. In 2012 , 5.161 cases of imported malaria were recorded in the European Union (incidence rate: 0.88 cases per 100.000) with the United Kingdom (UK) and France contributing to the majority of cases [2]. Of the five species responsible of naturally transmitted infections in humans, *Plasmodium falciparum* is recognized as causing most of imported malaria cases in Europe and because infection with this micoorganism may rapidly evolve to a life-threatening multi-system organ disease it is associated with almost all cases which require admission to the intensive care unit (ICU) [3-5]. Analysis of large database from France and UK showed that case-fatality rate associated with *P. falciparum* malaria was in the order of 0.4 % and 0.73 %, respectively [5,6]. However, ICU mortality in severe cases of *P. falciparum* infection is reported to be in the average of 5 to 10% [3,8,9]. Furthermore, a study of all malaria cases reported to the Centers for Diseases Control in the USA from 1985 to 2011 showed that *P. falciparum* was ten times as likely to cause death when compared with *P. vivax*, with a case-fatality rate of 0.9% [10].

In Western countries the risk of severe *P. falciparum* malaria and death was shown to be associated with several factors such as initial misdiagnosis [11,12], patient delay to seek medical attention, the time required to obtain a diagnosis of malaria and delays in treatment inception and appropriateness [13].

The present paper aims to review the clinical aspects of, and the management strategies used in, patients with severe *Plasmodium falciparum* malaria admitted to the intensive care unit (ICU) of a University hospital in Milano, Italy during a 6-year period.

2. Patients and methods

The Luigi Sacco Hospital (LSH) in Milano is a 550-bed Academic hospital that serves as a referral centre for patients with imported tropical diseases, including malaria. It has 2 infectious disease units with 76 inpatient beds and an 8-bed multidisciplinary ICU.

The records of all patients with severe *P. falciparum* malaria admitted to the ICU of LSH from January, 2010 to December, 2015 were retrospectively reviewed.

Severe and complicated malaria was defined according to the 2000 World Health Organization criteria [14]. In brief, in the presence of asexual forms of *P. falciparum* in the blood, the presence of one of more of the following features defines severe malaria: 1) impaired consciousness (Glasgow Coma scale < 11); 2) pulmonary oedema or adult respiratory distress syndrome; 3) circulatory collapse (systolic blood pressure< 80 mmHg despite adequate volume repletion); 4) severe anaemia with a haemoglobin level < 7 g/L (in adult patients); 5) hypoglicaemia with a blood glucose level < 40 mg/dL; 6) abnormal bleeding and/or disseminated intravascular coagulation (DIC); 7) renal failure with a serum creatinine concentration > 3 mg/dl and/or a 24-hour urine output of < 400 mL despite adequate re-hydration; 8) acidosis (blood pH < 7.35 or a serum bicarbonate level < 15 mmol/L or hyperlactataemia (plasma lactate level > 5 mmol/L); 9) jaundice or total bilirubin level > 3 mg/dL; 10) hyper-parasitemia (parasite count > 5%); 11) repeated generalized seizures; 12) hemoglobinuria.

Acute lung injury was defined as the acute onset of bilateral pulmonary infiltrates on chest X-ray or CT scan with a PaO_2/FIO_2 < 300 mmHg, regardless of positive end-expiratory pressure (PEEP) levels. Patients with acute lung injury and a PaO_2/FIO_2 below 200 mmHg were classified as having ARDS [15].

Parasite counts were calculated as the percentage of parasitized red blood cells (RBC) observed by direct microscopy in a thin blood film. The treating physician ordered serial peripheral blood film examinations during the clinical management of patients with a frequency that was at his discretion and until malaria parasites could not be observed any longer.

The decision to employ red blood cell exchange was taken by the treating physician, in conjunction with specialists in transfusion medicine.

Three prognostic malaria scores were calculated for each patient admitted in the ICU, namely the Malaria Score for Adults (MSA), the Coma Acidosis Malaria (CAM) scoreand the Malaria Severity Score. Malaria Score for Adults (MSA) is obtained by the sum of the following conditions each assigned a pre-definite point and ranges from 0 to 10: 1 x (severe anemia [haemoglobin level < 5 g/dL]) + 2 (acute renal failure [creatinine level>3 mg/dL])+ 3 (respiratory distress, requiring mechanical ventilation)+ 4 x (cerebral malaria, [GCS < 11V), in which each variable was scored as 0 or 1 [16]. Coma Acidosis Malaria (CAM) score is calculated as the base deficit score (0-2) as follows : base deficit < 2 =0; 2 to < 10= 1; > 1=2 plus the Glasgow Coma Score (GCS; 0-2): 15=0; > 10 to 14=1; < 10=2. Respiratory rate-based CAM score (0-4) is calculated as the respiratory score (0-2) as follows : respiratory rate < 20=0; 20 to <40=1; > 40=2 plus the GCS score (0-2) as previously described [17].

The Malaria Severity Score that defines dysfunction in 7 organ systems with 3 levels of severity and assigning 1, 3 and 5 points to level I, II and III severity of organ dysfunction respectively. The score ranges from 0 to 21 with risk of mortality calculated for each score [18].

Clinical severity at ICU admission was also assessed using the APACHE II score [19], SAPS II score [20] and SOFA score [21].

3. Results

Between January 2010, and December 2015, 177 adult patients with 180 diagnosis of malaria were cared for at the LSH in Milano (data not shown). Except for 30 *P. vivax,* seven *P. ovale* , four *P. malariae* and three mixed *P. falciparum –P. vivax* infections, all other patients (136, 75.5%) suffered from *P. falciparum* malaria.

Twelve patients (6.6%), with a median age of 43 years (range 28-59 years) were admitted to our ICU due to the presence of clinical and laboratory features of severe *P. falciparum* malaria according to WHO criteria (Table 1). Seven patients were male and five female ; except for 4 African patients all were Italians. Upon admission to the ICU, 3 patients (25 %) had 5 or more WHO criteria for severe malaria while during the ICU stay 6 additional patients developed one or more WHO criteria for severe malaria.

Five patients were admitted directly to the ICU from our Emergency Department (ED), four were transferred from the ED of neighbouring hospitals, two were transferred from the infectious diseases and internal medicine departments of our Hospital and one was airlifted from Africa and directly hospitalized to our ICU upon arrival in Italy.

All individuals had acquired the infection in sub-Saharan countries of West or Central Africa: 3 from Senegal, 2 from Nigeria, 2 from Cameroon, 2 from Ivory Coast and 1 each from Congo, Sierra Leone and Uganda). Eleven patients were returning to Italy while one was visiting our country for the first time. The main clinical and epidemiological characteristics of each patient are summarized in Table 1. Of note, none of them had taken antimalarial chemoprophylaxis. In all patients who were diagnosed with malaria while in Italy (n=11) symptoms appeared within a median of 10 days (range 8-14 days) from arrival. The median time between symptoms onset and the time when patients first sought medical attention was 3.5 days (range 1-13 days) and corresponded in all cases but three (patient # 10 #11 and #12), with the time when the diagnosis of malaria was made. The 3 patients in whom the diagnosis of malaria was initially overlooked were

either discharged by the ED without ruling-out a diagnosis of this infection or, in one case, were hospitalized with an erroneous diagnosis (acute pyelonephritis).

The median delay with which the diagnosis of malaria was made in these patients was 8 days (range 3-9 days). For all other individuals who were correctly diagnosed at the first observation, the median time from presentation to the ED and the parasitological diagnosis of malaria was 2.7 hours (range 1,16-9,30 hours) while the median time elapsing from the parasitological diagnosis of malaria and the first dose of quinine administered was 2 hours (range 1,20-4,30 hours). Globally, the median time from presentation to the hospital and the beginning of antimalarial therapy was 4,45 hours (range 2,36-14 hours).

The median length of hospitalization was 11,5 days (range 8-43 days) and the median time spent in the ICU was 5 days (range 1-21 days). The median number of WHO criteria for severe malaria observed at the time of admission was 3 (range 1-8) and during stay in ICU 2.5 (range 1-4) additional criteria of severe malaria developed. Jaundice was present in ten patients (83.3%), shock in four (33,3%). Specifically, while in ICU, five patients developed ARDS a median of 3 days after admission and in additional two shock ensued. Impaired consciousness was present at the time of hospitalization in 4 patients (33.3%). Acute renal failure with oligo-anuria was observed in 4 patients (33.3%) and required in all cases renal replacement treatment.

The two patients with low levels of parasitaemia (#6 and #10) were notable in one case for the development of severe anemia (Hb 6.9 g/dL) and highly elevated levels of transaminases (AST 676 U/L, ALT 646 U/L), LDH (713 U/L) and bilirubin (13,4 mg/dL) and in the other for the severe renal failure and the development of ARDS requiring mechanical ventilation on the third day of ICU hospitalization.

Thrombocytopenia was the haematologic alteration observed in all patients (median value 29,000/μL, range 7000-68.000/μL); anemia was present in 10 patients (median Hb 8.4 g/dL, range 6.5-14.5 g/dL) in 10 patients and was classified as severe in three patients. Other relevant laboratory parameters (Table 2) were: hyponatriemia, present in 11 patients with a median value of 131

mmol/L (range 122-134 mmol/L); hypoalbuminaemia, detected in all patients (10) for whom this data was available (median 2200 mg/L, range 1400-2600 mg/dL) and hyperlactataemia (> 5 mmol/L) observed in two patients.

Four patients received inotropic drugs and five mechanical ventilation (median 7 days, range 3-14 days). Nine patients received blood transfusions although only two fulfilled strict criteria for severe anemia. Two patients underwent blood exchange transfusion with, respectively, 1500 and 3000 mL of red blood cells and fresh frozen plasma and one patient underwent erythrocytapheresis. Two patients received platelet transfusion.

3.1 Kinetic of parasite clearance times

Sixty-eight examinations of peripheral blood were performed (a mean of 5.7 determinations per patient). High parasitaemia (≥ 5%) was observed at baseline in ten patients (83,3%) with a median value on the first day of 14.5 % (range 1,0-20 %). Patient # 2 after the initiation of antimalarial treatment had a marked increase of parasitaemia (27%) that prompted the start of blood exchange transfusion with a rapid decrease (1%) within the next 12 hours. The other two patients (# 8 and #9) who underwent erythrocytapheresis or blood exchange transfusion had a drop of parasitaemia from the baseline level (20 and 17%) to 0,5% within 24 hours.

The median time required to achieve a negative blood parasitemia in all 12 patients was 77 hours (range 54-144 hours).

3.2 Scores of severity

In table 2 are shown the different scores calculated upon admission in the ICU for all patients (patient #4 had 2 admission in the ICU). Patient # 5,8,9 and 10 had the highest scores using the APACHE II, SAPS II and SOFA scores with the corresponding highest predicted mortality. The same patients were identified with the highest scores by MSA, MSS and CAM with the exception of patient #10 who had lower scores with MSS and CAM. Also for patient # some discrepancies

with the application of different scores were observed. It seems that all scores were able to identify patients with very severe malaria but they overestimate mortality prediction.

3.3 Treatment

All patients admitted to the ICU received intravenous quinine dihydrochloride treatment with a loading dose of 20 mg/kg body weight administered over 4 h followed by 10 mg/kg body weight every 8 h until they were able to take oral medication. Six patients completed oral antimalarial therapy either with quinine (n=4 patients) or with dihydroartemisinin-piperaquine (n=2 patients). At discretion of the caring physician, nine patients also received intravenous or oral doxycycline at a dose of 100 mg every 12 hours for seven days.

All patients survived and at the time of discharge all complications related to severe malaria resolved except for mild renal insufficiency in two individuals and persistent renal failure in one patients who is, at the time of writing, still under renal replacement therapy.

4. Discussion

In this retrospective study, we describe 12 consecutive patients with severe *P. falciparum* malaria (in one case associated with *P. vivax*) who were admitted to our ICU. Altogether, they represent 6.6% of all cases of *P. falciparum* malaria observed at LSH who were admitted to the ICU during a 6-year period. Consistent with a recent review of the literature regarding adults patients with *P. falciparum* malaria requiring intensive care, all our patients acquired the infection in sub-Saharan Africa and none of them had taken chemoprophylaxis [3]. The latter issue is particular worrisome because among these patients three had long-term working experience in malaria-endemic areas and another three volunteers engaged in humanitarian aid programmes with multiple and prolonged period of stay in Africa, both conditions that should have raised their awareness of the risk of contracting malaria.

The median time from patient symptom onset to healthcare access was in our experience 3.5 days that is exactly the same interval reported in the two largest single centre studies of imported *P. falciparum* malaria requiring ICU admission [22,23].

In a study conducted in the USA regarding malaria deaths among travellers, failure to take chemoprophylaxis or to seek medical attention promptly, together with medical errors, were considered the variables associated with 85% of preventable deaths [13]. In fact, three patients who developed complications of severe malaria were initially misdiagnosed at the ED .It is tempting to speculate whether a correct diagnosis would have avoided these patients both the ICU admission and the subsequent complications.

Although our study was retrospective, we had the opportunity to evaluate two key elements in the management of patients with severe malaria, namely the interval of time from initial evaluation at the ED to the diagnosis of malaria and the time elapsed between diagnosis of the disease and the beginning of antimalarial treatment with intravenous quinine. The median values for these intervals were, respectively, 2.7 and 2 hours. It is well known from experience in other severe infections that a delay in starting the appropriate antimicrobial therapy is associated with a worse outcome but we are not aware of any study of severe malaria where the interval time from diagnosis to beginning of specific therapy was associated with patient outcome. We wonder whether the relatively short intervals of time recorded in this study may in part explain the favourable outcome observed in our patients. Although we believe that our results are indicative of a high level of suspicion regarding malaria infection among physicians in our hospital, we acknowledge that there is still room for improvement in both temporal variables.

Even when high quality healthcare is available, the mortality rate in adults associated with imported severe *P. falciparum* malaria ranges from 5% to 10.5 % [8,23]. In a prospective multicenter study conducted in France from 2007 to 2010, Bruneel *et al.* showed a trend toward a lower mortality in comparison with their previous study (from 10.5% to 5.2%) but this figure is still somewhat elevated. By contrast, in the TropNet severe malaria study the overall mortality rate was 1.6% with

no significant differences among patients treated with artesunate (1.6%) and quinine (2.2%) [24,25]. However, the results of two large comparative trials conducted in Asia and Africa (AQUAMAT and SEQUAMAT), showed that parenteral artesunate, reduced mortality among adults and children when compared with quinine, and for this reason the former is now recommended as the drug of choice for the treatment of severe *P. falciparum* malaria [26,27]. Nevertheless, in non-endemic areas it is still controversial whether intravenous artesunate, despite being associated with faster parasite clearance rates and more rapid resolution of fever and shorter ICU stays, is capable to further reduce malaria mortality [28]. In this regard, three recently published studies from Belgium and the Netherlands, USA and France report mortality rates among patients with severe malaria treated with intravenous artesunate of, respectively, 3.6 %, 6.9% and 4.9% [29-31]. However, we agree with the statements by Roussel et al. who recently reviewed the role of artesunate in the treatment of severe malaria in travellers [32]. In Europe, the drug need to be submitted to full good manufacturing practice (GMP) qualification followed by a rapid approval by European Medicines Agency (EMA) in order to be available as first choice therapy of severe malaria.

Red blood cell exchange an adjunctive treatment employed to rapidly clear peripheral blood parasitemia in severe malaria has not yet been shown, to our knowledge, to confer an improvement in patient survival. Indeed, this intervention was recently shown not to provide faster parasite clearance rates in patients currently treated with intravenous artesunate [33-35]. We used RBC exchange in three patients with very high parasitemia but despite rapidly achieving fast reduction we cannot made any conclusion.

Severe *P. falciparum* malaria is defined by the World Health Organization (WHO) criteria which were formulated with the objective to identify those patients who would benefit from intensive monitoring and parenteral antimalarial treatment. However, in this regard, not all criteria display the same capacity to identify patients with a poor prognosis as well as patients who will benefit for immediate admission to the intensive care unit. In the 400-patient cohort study conducted in France by Bruneel *et al*., three variables present at ICU admission independently predicted death: older

age, coma and high parasitemia [8]. Identifying patients with severe imported malaria at high-risk of death in ICU is of paramount importance.

Three recently described scoring systems- Coma Acidosis Malaria (CAM) score, Malaria Score in Adults (MSA) and Malaria Severity Score (MSS) were proposed in order to predict mortality risk of *P. falciparum* malaria in adults [16-18]. All these scores have been validated in studies conducted in South-East Asia [17] and India [16,18] where the standard of intensive care are probably not the same of Europe. The AUROC (area under the receiver operating characteristic curve) for the MSA score and CAM score for predicting death (applied to patients enrolled in the SEAQUAMAT) were 0.75 and 0.81, respectively [17].However, the high positive predictive value of both scores, 95.8% for CAM (with a score of less than 2) and 94.1% for MSA (with a cut-off of 5) were more predictive of survival than death. Marks *et al.* applied the CAM and MSA score to 124 patients with severe *P. falciparum* malaria admitted to their ICU in London showing, in agreement with the above cited results, that these scores performed poorly in predicting mortality [23]. In another retrospective study conducted in Portugal among 59 patients with severe malaria admitted to the ICU, SAPS II and WHO score were the most sensitive in predicting death with an AUROC of 0.90 and 0.91, respectively [36].

In our study, the application of CAM, MSA and MSS scores to a small series of patients with severe *P. falciparum* malaria admitted to the ICU showed that all of them had limited utility in estimating mortality risk being, at best, useful to assess the severity of malaria. In our opinion it is more useful the definition adopted by Bruneel *et al.* that among patients fulfilling the 2000 WHO criteria for severe malaria in adults identified two subgroups: those with very severe malaria (VSM) experiencing coma, shock, acidosis, hyperlactatemia (>5 mmol/L) or respiratory distress within the first 72 hours of the ICU and those with less severe malaria (LSV) (*i.e.*, with none of the above criteria) [9]. In their valuable work the French authors showed that death occurred only in the subgroup of patients with VSM (mortality rate 10.5%) while all subjects with LSM survived [9]. Interestingly, they noted that the best biomarkers associated with severity were plasma albumin and

soluble triggering receptor expressed on myeloid cells (sTREM-1) [9]. By contrast, in another study of imported malaria, te Witt *et al*. failed to demonstrate any discriminative power of TREM-1 levels measured upon hospital admission among patients with severe and uncomplicated *P. falciparum* malaria [37]. The same group showed that hyponatremia (with a value of < 131 mmol/L) was independently associated with severe falciparum malaria (OR 10.4) [38]. In our study, both hypoalbuminemia and hyponatremia were observed among patients with severe falciparum malaria and we believe that their widespread availability make them more attractive than other proposed biomarkers of malaria severity. Finally, we would like to highlight that 33% of patients admitted to our ICU with severe malaria were either VFR or migrants from highly endemic malaria areas . This observation adds to debate over the duration of malaria semi-immunity of individuals from endemic areas and their resistance to severe malaria development [39-41]. Although it is generally acknowledged that individuals arriving from endemic areas tolerate higher levels of parasitaemia with fewer complications, one of our patient developed severe malaria despite a parasitaemia below the threshold considered at risk of severe malaria. We therefore would like to warn against considering recently arrived migrants from malaria-endemic areas as individuals not at-risk for severe malaria development and thus eligible for outpatient treatment of the disease [42].

4.1 Conclusions

Our recent experience regarding the treatment of severe imported *P. falciparum* malaria in a small series of adult patients suggests that even those with more severe picture can have a favourable outcome if managed in an high specialized centre. We confirm that ARDS, one of the more feared complication tend to occur later respect other complications. Scores commonly used in the ICU and those developed for malaria seems able to recognize patients with more severe malaria but overestimate mortality risk. We believe that host presentation with shock or coma, high parasite biomass (detected by day 1 peripheral parasitaemia or plasma PfHRP-2 as recently suggested by Bruneel et al) together with lactic acidosis and hypoalbuminemia are the parameters associated with more severe malaria.

Conflict of interest

All the Authors no conflict of interest to disclose

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Table 1- Epidemiologic, clinical and laboratory features of 12 patients with severe *P. falciparum* malaria admitted to the ICU

Patient N°	Sex, age	Reason for travel	Country of origin/ Country of disease acquisition	Prophylaxis/ Therapy	WHO criteria for severe malaria on ICU admission/ Criteria developing after ICU admission	Time from symptom onset to health-care presentation (days)	Time from initial evaluation to diagnosis (hours)/ Time from diagnosis to treatment (hours)	Parasite level (initial)	Blood transfusion (N° RBC Unit)/ Platelet transfusion (N° Unit)	Inotropic drugs/ Mechanical ventilation (days)	Exchange transfusion (N° RBC unit/FFP)	CVVHDF (days)	Days in ICU/ Total hospital days
1	M,33	VFR	Nigeria/ Nigeria	ND/Quinine iv+ doxycycline	H/None	3	4,20/1,20	5%	No/No	No/No	No	No	4/8
2	M,40	Work	Italy/ Cameroon	ND/Quinine iv+ doxycycline	H, J/IC	6	3,30/2,00	5,8 %	Yes (3)/No	No/No	Yes (4 / 5)	No	3/13
3	F,59	Volunteer	Italy/Ivory Coast	ND/Quinine iv (2 d) then po+ doxycycline	H/None	4	2,35/2,00	5,4%	No/No	No/No	No	No	1/9
4	F,31	Recently immigrated	Senegal/ Senegal	ND/Quinine iv	H,J,S,A,D, Hy/ARDS	2	2,40/2,00	20 %	Yes (4)/No	Yes/Yes (4)	No	No	6 (1+5)/ 14
5	M,47	Work	Italy/Nigeria	ND/Quinine iv (3 d) then po	IC,S,RF,H,J,A /ARDS	3	NA	15%	Yes (4)/No	Yes/Yes (7)	No	No	9/23
6	M,45	Volunteer	Italy/Congo	ND/Quinine iv	J, D ,He/SA	7	5,00/1,30	1,5%	Yes (4)/No	No/No	No	No	1/9
7	F, 42	Volunteer	Italy/Sierra Leone	ND/Quinine iv (2 d) then po+ doxycycline	H, J, D/None	4	9,30/4,30	14%	Yes (2)/Yes (1)	No/No	No	No	3/10
8	M,52	Work	Italy/Senegal	ND/Quinine iv+ doxycycline	H, J, S, A, He, ,IC,RF/SA, ARDS	5	3,00/1,45	20%	Yes (5)/No	Yes/Yes (14)	Yes (4 /5)	Yes (21)	21/43
9	F,44	Tourism	Italy/Uganda	ND/Quinine+ doxycycline	H,J, IC,A/S, ARDS, RF, Hy	13	1,30/2,30	17%	Yes (2)/Yes (1)	Yes/Yes (7)	Yes* (6+6)	Yes (12)	13/32
10	M, 41	VFR	Mali/Ivory Coast	ND/Quinine iv+ doxycycline	J,RF/ARDS, SA	(1)**3	1,16/1,20	1%	Yes (3)/No	No/Yes (3)	No	Yes (6)#	6/24

11	M,28 §	Work	Italy/ Cameroon	ND/Quinine iv (2d) then DHAP+ doxycycline+ primaquine	H, J/SA	(1)**9	2,30/2,25	20%	Yes (3)/No	No/No	No	No	6/10
12	F,44	VFR	Senegal/Senegal	ND/Quinine iv (3) then DHAp+ doxycycline	S,H,J,SA/None	3*** (8)	ND	15%	Yes/No	No/No	No	No	1/8

VFR, visiting friends and relatives; WHO, World Health Organization; ICU, intensive care unit; RBC, red blood cell; FFP, fresh frozen plasma; CVVHDF, continuous venous-venous hemodiafiltration; H, hyperparasitaemia; J, jaundice; D, disseminated intravascular coagulation; S, shock; ARDS, adult respiratory distress syndrome; RF, renal failure; IC, impaired consciousness; A, acidosis; Hy, hypoglicemia; He, hemoglobinuria; SA, severe anemia; ND, not done; NA , not available. * Erythrocytapheresis; ** Both patients initially evaluated at ED of other hospital and discharged with a diagnosis of "viral syndrome"*** This patient was initially hospitalized in an Internal Medicine ward with a diagnosis of pyelonephitis;; § This patient had concomitant *P. vivax* infection;# hemodialysis thrice weekly until discharge with serum creatinine 6.6 mg/dL; IV, intravenous; po, orally; DHAp, dihydroartemisinin-piperaquine

Table 2- Laboratory findings and severity scores of 12 patients with severe *P. falciparum* malaria at the time of admission to the ICU

Patient	1	2	3	4*		5	6	7	8	9	10	11	12	Median
Age	33	40	59	31		47	45	42	52	44	41	28	44	43
Temperature	39	39	36	39	38,3	40	39,3	40	38,2	39	38,5	39,5	40	39
Mean arterial pressure mm Hg	90	110	75	75	78	50	80	90	60	55	115	70	90	78
Ph (arterial)/lactate	7,44/0,7	7,46/4,8	7,40/1,3	7,33/2,7	7,36/1,4	7,17/8,4	7,41/1,4	7,48/2,2	7,27/6,6	7,09/>15	7,38/2,6	7,45/2,6	7,45/2,3	7,405/2,6
HCO3- mmol/L	26,5	20,6	31	24,3	28,2	14,9	27,3	18,4	16,5	15,8	19	22,9	20,2	20,6
Heart rate	85	100	84	110	110	140	110	94	150	125	110	118	100	110
Respiratory rate	22	20	20	24	60	36	28	24	35	35	22	30	21	24
Sodium, mmol/L	133	131	129	130	133	140	131	124	122	134	130	122	132	131
K+, mmol/L	3,6	3,7	3,0	4	3,8	3,9	4,2	3,3	4,8	3,8	3,9	4	3,6	3,8
Creatinine, mg/dL	0,93	1,23	0,53	1,19	1,08	4,24	1,48	1,09	5,41	7,27	8,89	2,31	2,06	1,48
Glucose	114	85	83	67	53	74	83	106	100	49	96	131	132	85
Hb, g/dL	14,5	9,6	11,1	9,2	8,6	8,4	6,9	10,4	8,4	7,1	8,4	6,5	7,0	8,4
Ht, %	44,8	24,3	25,8	26.6	25	24	19,8	28,6	24	20,7	23,3	17,8	21,5	24
Platelets/µL	13000	46,000	89,000	8,000	58,000	68,000	29,000	7,000	22,000	18,000	34,000	26,000	38,000	29,000
WBCs/µL	5420	5070	5100	4860	6320	15,940	1700	4230	14.170	10950	6650	8100	3890	5420
Bilirubin total mg/dL	1,35	4,38	1,14	15,9	4,75	6,98	13,4	5,18	10,16	14,4	17,1	5,95	7,08	6,98
D-dimer, ng/mL	520	>10.000	458	>10.000	1222	1271	9606	17781	>10000	7244	2850	6881	>10000	7244
Albumin mg/dL	NA	2600	NA	2900	-	1400	2200	1900	2400	1800	2200	2000	2800	2200
Glasgow Coma Score	15	11	15	15	8	3	13	13	10	10	15	14	15	13
APACHE II -Predicted mortality	7 7,6%	12 14,6%	10 11,3%	7 7,6%	17 26,2%	40 91.1%	14 18.6%	11 12,9%	31 73.3%	35 83.1%	38 82 %	17 26.2%	11 15%	14
SAPS II - Predicted mortality	15 2 %	31 11,7%	22 4,7 %	35 16,7 %	35 16,7%	90 96.7 %	41 26,6 %	41 26,6%	68 81,3%	64 75,3%	55 57.5%	50 46,1%	46 37%	41
SOFA -Predicted	5 <10%	9 15-20%	3 < 10%	12 40-50%	11 40-50%	19 > 90%	10 40-50%	8 15-20%	17 >90%	18 > 90%	12 40-50%	10 40-50%	11 40-50%	11

mortality														
MSA - Predicted mortality	0 2 %	4 40 %	0 2 %	7 90 %	3 40%	9 90 %	0 2 %	0 2%	9 90%	5 40%	5 40%	1 2%	2 2%	3
WHO > 5	No	No	No	No	No	Yes	No	No	Yes	Yes	No	No	No	3/12
MSS -Predicted mortality	1 3.1%	3 7.5%	0 1.2%	3 7.5%	9 51.8%	16 96.1%	5 12%	3 7.5%	12 81.8%	9 51.8%	7 31.1%	5 12%	6 21.1%	5
CAM	1	2	0	1	3	4	0	2	4	3	1	1	1	1
RCAM	1	2	1	1	4	3	2	2	3	3	1	2	1	2

SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; MSA, Malaria Score in Adults; WHO, World Health Organization; MSS, malaria Severity Score; CAM, Coma Acidosis Malaria Score; RCAM, Respiratory Coma Acidosis Malaria; * Patient admitted twice in ICU