MALARIAL ACUTE RENAL FAILURE AT MAE SOT GENERAL HOSPITAL, THAILAND: OUTCOME AND ASSOCIATED RISK FACTORS FOR DEATH AND DIALYSIS

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A THEMATIC PAPER SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF CLINICAL TROPICAL MEDICINE FACULTY OF GRADUATE STUDIES MAHIDOL UNIVERSITY 2008

Thematic paper
Entitled

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ACKNOWLEDGEMENTS

First I would like to thank my main advisor Dr. Vipa Thanachartwet. Her clinical experiences in tropical medicine and her expert knowledge in the field of nephrology as well as the countless suggestions, comments and contributions throughout the research- and writing-process were highly contributing to the success of this thematic paper.

Special thanks go to my co-advisor Associate Professor Yupaporn Wattanagoon for sharing her expertise and experience in the field of research and her knowledge in clinical malariology with me as well as for her unresting supportive supervision and guidance of this thematic paper.

I am specially thankful to my co-advisor Associate Professor Varunee Desakorn for her valuable support and expert advice regarding the planning and statistical workup of this study. Without her, the statistical outline of this paper would not have been possible.

I would like to thank my co-advisor Dr. Supat Chamnachanan for his consistently high quality support and the priceless tips and hints, which deeply contributed to the outline and form of this study.

I am deeply in dept to my "field"-co-advisor Dr. Ronnatrai Ruangweerayut, who dedicated so much time and efforts in advice, help and guidance throughout the process of this study. His dedication to clinical work as well as to clinical research was highly inspiring. I enjoyed our countless conversations not only on medical topics. He contributed to my view of clinical medicine far beyond the scope of this thematic paper. Special thanks go to his wife Kulya Ruangweerayut, who not only took care of my daily needs by her fabulous cooking skills (introducing and exposing me to the various sorts of spiciness in Thai cuisine) but also trained my eye in malaria microscopy.

I would like to express my gratitude to Senior Colonel Dr. Thanom Supaporn for his expert opinion on nephrology and for his highly valuable comments, suggestions and inspirations as external advisor of this thematic paper.

I would like to express my gratitude to all my advisors for their special efforts to introduce me to Thai culture, traditions, cuisine and many beautiful spots in Thailand during my studies. ขอบคุณมากๆ !

Special thanks go to my translators at Mae Sot General Hospital Mrs. Vilaiwan Jekuree and Mr. Suwat Loetunkaew. Without their indefatigable assistance and help throughout the data-collection- and file-translation-process the extensive workload would have not been accomplished.

I want to thank all lecturers of the Faculty of Tropical Medicine, who broadened my medical horizon and set the stage for this study and my further medical work. They will always be linked to my memories of the time I spent in Bangkok.

I am heartily thankful to the Roland-Ernst-Foundation for granting me a one-year scholarship for my training in Bangkok.

I am deeply in dept and specially thankful to Prof. Dr. med. Joachim Radke, who granted my leave of absence from my current workplace at the University Hospital of Halle-Wittenberg, Department of Anaesthesiology, Intensive Care and Emergency Medicine for my one year master training in tropical medicine.

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This retrospective study was conducted to determine the case fatality rate among malarial-acute-renal-failure (MARF) patients at Mae Sot General Hospital, to identify putative risk factors for a fatal outcome, the need for renal replacement therapy (RRT) and RRT outcome. Between 1 January 2002 and 31 December 2007, 412 severe malaria cases were admitted, of whom 76 MARF cases fulfilled the study inclusion criteria. The overall case fatality rate was 26.3%, which was significantly higher among referred cases than the directly admitted cases (36.8% vs. 15.8%; $p = 0.037$). The highest case fatality rate (50%) was among patients referred by NGOs. 32 (42.1%) of the 76 MARF patients received RRT (16 were treated with hemodialysis (HD), 10 with peritoneal dialysis (PD), and 6 with PD and HD). The median (range) of dialysis cycles and duration of treatment in patients successfully treated with HD was 2.5 (1-9) cycles and 8 (1-13) days. Impairment of consciousness, GCS < 10, circulatory collapse, mechanical ventilation, FFP transfusion, high white-blood-cell (WBC) counts and high aspartate-amino-transferase (AST) levels were significantly associated with fatal outcome for MARF patients ($p < 0.05$), irrespective of RRT. These factors were also significantly associated with the use of RRT in MARF patients ($p < 0.05$). In addition, the MARF patients who died had significantly higher rates of metabolic acidosis, lower serum protein and serum globulin levels, more frequent hepatomegaly and higher ALT levels ($p < 0.05$). High serum potassium, low sodium and chloride levels, and prolonged PTT at admission were other factors significantly associated with a fatal outcome in the group receiving RRT. These may represent MARF patients who arrived for treatment too late, and may not have been saved even with immediate RRT and intensive medical care. However, logistic regression analysis showed that the remaining factors significantly associated with death were "mechanical ventilation" (OR = 154.9; $p = 0.028$) and lower "serum globulin" levels (OR = 0.017; $p = 0.017$). "Circulatory collapse" (OR = 27.00; $p = 0.035$) remained the only factor significantly associated with RRT among MARF patients.

KEY WORDS: ACUTE RENAL FAILURE / MALARIA / DIALYSIS / OUTCOME / RISK FACTORS

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACT	Artemisinin-based combination therapy
AIN	acute (tubulo-) interstitial nephritis
ALI	Acute lung injury
ALP	Alkaline phosphatase
ALT	Alanin-Aminotransferase
APACHE	Acute physiology and chronic health evaluation
ARDS	Acute respiratory distress syndrome
ARF	Acute renal failure
AST	Aspartat-Aminotransferase
ATN	Acute tubular necrosis
BP	Blood pressure
BUN	Blood urea nitrogen
CPK	Creatin-Phosphokinase
CSF	Cerebrospinal fluid
CRRT	Continuous renal replacement therapy
CVVH	Continuous veno-venous haemofiltration
DIC	Disseminated intravascular coagulation
FCT	Fever clearance time
FFP	Fresh frozen plasma
Hb	Haemoglobin
Hct	Haematocrit
HPF	High power field
GCS	Glasgow coma scale
G6PD	Glucose-6-phosphate dehydrogenase
HES	Hydroxyethyl starch
ICU	Intensive care unit
INR	International normalized ratio

LIST OF ABBREVIATIONS (CONT.)

Abbreviation	**Term**
iRBC	Infected red blood cells
LDH	Lactate-Dehydrogenase
LPF	Low power field
MARF	Malaria associated renal failure
MAS	Malaria score for adults
MODS	Multi-organ dysfunction score
MPGN	Mesangioproliferative glomerulonephritis
MSA	Malaria score for adults
MSF	Médecins Sans Frontières
NGO	Non-government-organisation
NO	Nitric oxide
pH	Potential of hydrogen
PIGN	Postinfectious glomerulonephritis
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
RRT	Renal replacement therapy
SEAQUAMAT	South East Asian Quinine Artesunate Malaria Trial
SD	Standard deviation
TNFα	Tumour necrosis factor alpha
UPCI	Urine Protein Creatinine Index
URL	Uniform resource locator
vs.	versa
WBC	White blood cell
WHO	World Health Organisation

CHAPTER I
INTRODUCTION

Malaria has been a described disease since antiquities and probably accompanied mankind throughout all ages (Winkle, 2005). Since the first reported observation of parasitic organisms in red blood cells by Charles Louis Alphonse Laveran in 1880, malaria has kept researchers and physicians busy down to the present day. Despite the enormous advances and gains in parasitological, entomological and pathophysiological knowledge, the achievements in medical diagnosis and treatment and the large worldwide eradication programs and anti-malaria campaigns throughout the last century, malaria remains the most important parasitic disease of man (White, 2003a). Encouraged by the early demonstration of successful eradication campaigns, eradicating malaria from the United States in the early 1950s and from Europe in the 1960s, the World Health Organisation (WHO) initiated the "Global Eradication of Malaria Program". Consecutively malaria was successfully eradicated or reduced in wide regions of the tropics between 1955 and 1970, before the program was finally officially declared failed and abandoned in 1972.

With the development of insecticide-resistant mosquito vectors, the emerging of multi-drug-resistant malaria parasites, global ecological changes with the introduction and reintroduction of the vector and the parasite to new areas and old regions - where malaria was eradicated in the past - and the increase of global travel, malaria is a major social and economical burden for many developing countries and a challenge not only for physicians in the tropics (Kain and Keystone, 1998; Sachs and Malaney, 2002).

Today approximately 2.5 billion people, 40% of the world's population - mostly those living in the world's poorest countries - are at risk of malaria. The WHO estimates a number of 300 to 500 million clinical malaria cases, with at least one million deaths annually (WHO, 2007). This figure, based only on reported cases, probably underestimates the real number of malaria attributed deaths, and is frequently estimated to be as high as three million cases (Bruneel et al., 2003; Pasvol, 2005a; Ladhani et al., 2007).

From the four human pathogen Plasmodium species almost all malaria deaths can be attributed to *Plasmodium falciparum*, as death from acute *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae* infections is very rare (White, 2003a).

In general malaria infections are often classified in "uncomplicated malaria" and "complicated malaria". To assess the high morbidity and mortality linked to complicated *P. falciparum* infections the WHO released criteria for recognition of severe forms of malaria infections in 1990 and added some modifications in 2000 (WHO, 1990; WHO, 2000). The last published and currently used WHO-criteria for "severe malaria" were published in October 2006 and are shown in Table 1 below (WHO, 2006b). There is no clear differentiation between the terms "severe malaria" and "complicated malaria" and both terms are frequently used interchangeably as synonyms. While "severe malaria" is commonly defined by the WHO-criteria, "complicated malaria" can refer to any unusual clinical presentation or complication in the course of a malaria infection.

The major complications - and causes of death - in patient with severe malaria include severe anemia, cerebral malaria, acute renal failure (ARF), respiratory failure and/or bleeding. Acidosis and hypoglycaemia are the most common manifestations of metabolic complications (Trampuz et al., 2003). Any of these complications can be present alone or in combination, develop rapidly and progress to death within hours or days (WHO, 2000). The mortality of untreated severe *P. falciparum* associated malaria probably approaches 100% (White, 2003b).

The clinical picture and the age distribution of severe malaria varies with endemicity and intensity of transmission. In areas of high and stable transmission rates (hyper- and holoendemic areas), severe malaria is confined mostly to children (with the main clinical impact of severe anemia in the first three years of life), while indigenous adults usually do not develop symptoms and never develop severe malaria because of acquired premunition. In areas with low, unstable and seasonal transmission patterns (hypoendemic areas) symptomatic infections are the rule, as no premunition is attained, and the age distribution shifts towards older age-groups, with cerebral malaria dominating the clinical picture of severe malaria. At very low levels of malaria transmission severe malaria may occur at all ages (White, 2003a). The observed frequency of complications in severe malaria is unevenly distributed in different age-groups: Clinical manifestations rarely seen in children, e.g. ARF, pulmonary oedema and severe jaundice are common in adult patient, whereas severe anemia is frequently found in children but an unusual complication in adults (White, 2003a).

Before 1980, the case fatality rate of severe malaria was around 29 to 40%, and only reducible with the increasing availability of intensive-care facilities, providing sophisticated supportive treatment, mainly through mechanical ventilation and renal replacement therapy (Stone et al., 1972; Punyagupta et al., 1974; Trang et al., 1992; Wilairatana et al., 1999).

A breakthrough in treatment of severe malaria was the introduction of Artemisinin-derivatives (extracted from the leaves of the shrub *Artemesia annua* [Chinese: "Qing hao"]) in clinical practice in the 1990s. In the SEAQUAMAT study - the largest ever clinical drug trial in severe malaria, including 1461 patients in four South and Southeast Asian countries between 2003 and 2005 - patients with severe malaria receiving intravenous Artesunate showed a 35% lower case fatality rate compared with patients receiving intravenous Quinine, the long-run drug of choice for severe malaria (Dondorp et al., 2005).

Besides the use of antimalarial drugs many adjuvant medications have been tried in order to improve the outcome of severe malaria (e.g. antipyretics, pentoxifylline, hyperimmune serum, deferoxamine, corticosteroids, anti-TNFα-antibodies, dextran, mannitol, heparin, etc.), but so far adjuvant medications have either shown to be controversial, ineffective or even harmful to the patients (Warrell et al., 1982; Kwiatkowski et al., 1993; Warrell, 1999; Looareesuwan et al., 1999). The quest for potential adjunctive treatment options is still ongoing as presented by a recent study evaluating the effect of Levamisole on infected red blood cell sequestration (iRBC). This study has shown that Levamisole is able to decreases iRBC sequestration in uncomplicated falciparum malaria in vivo by inhibiting the binding of iRBC to CD36, the major vascular receptor involved in the sequestration process. Whether this promising new approach will be effective in severe falciparum malaria has to be evaluated by further studies (Dondorp et al., 2007).

At the beginning of the 21st century the case fatality rate of severe malaria is still between 15 and 30% and it has to be shown in the future, how much this can be reduced by the implementation of Artemisinin-based combination therapy, by the increase in availability of intensive-care facilities in endemic areas or the longed for, but still far away option of an effective malaria vaccine (Krishna et al., 1994; Waller et al., 1995; Tran et al., 1996; van Hensbroek et al., 1996; Schellenberg et al., 1999; Day et al., 2000b; Planche et al., 2003; Mockenhaupt et al., 2004).

Table 1: World Health Organization criteria for severe malaria 2006 (WHO, 2006b).

Clinical manifestations	**Recognition**	**Laboratory findings**
Impaired consciousness	Assessment by Glasgow Coma Scale (10 or less) or Blantyre Coma Scale (3 or less) as appropriate	Normal cerebrospinal fluid (CSF)
Severe pallor	Conjunctiva, tongue, lips and palms are pale	Haemoglobin <5g/dl or Haematocrit <15%
Oliguria or anuria / Acute renal failure	Urine output <400ml/24 hours in adults and <0,5ml/kg/hour in children	Serum creatinine >3mg/dl in adults and >1,5mg/dl in children
Jaundice (combined with evidence of other vital organ dysfunction)	Yellow discolouration of sclera	Serum bilirubin >3mg/dl
Circulatory collapse, cold extremities, weak peripheral pulse	Cold, clammy, cyanotic skin and extremities, weak peripheral pulse and hypotension (systolic BP <80mmHg in adults and children over 10 years; <70mmHg in children aged 1 months to 10 years; <60mmHg in neonates); core/skin temperature difference of >10°C	
Metabolic acidosis	Laboured hyperventilation with increased inspiratory effort (often termed respiratory distress) and a clear chest on auscultation (Kussmaul's breathing)	Arterial pH <7,35 or plasma bicarbonate <15mmol/l; venous lactate level of >5mmol/l
Pulmonary oedema and or acute respiratory distress syndrome (ARDS)	Tachypnoe, dyspnoea and bilateral basal rales	Bilateral infiltrations in the lungs on chest film
Multiple convulsions	Jerky limb movements and staring eyes; two or more convulsions in 24 hours	Normal CSF
Spontaneous bleeding	Gums, nose, venepuncture sites, gastrointestinal tract	Blood tests suggestive of disseminated intravascular coagulation (DIC)
Haemoglobinuria	Dark red or black coloured urine	Urine is positive for haemoglobin
Hypoglycemia	Anxiety, sweating, palpitation, dilatation of pupils, breathlessness, convulsions, alteration of consciousness	Blood sugar <40mg/dl or 2,2mmol/l
Hyperparasitemia		Parasite density higher than 250.000/µl blood or infected red blood cells more than 5% in non-immune patients (20% in any patient) and appearance of peripheral schizontaemia
Prostration	Unable to feed, sit, stand, walk unaided	

CHAPTER II
LITERATURE REVIEW

Renal involvement in malaria infection

There are two major renal syndromes associated with malaria:

1. "Chronic quartan malaria nephropathy"
2. "Acute falciparum malaria nephropathy"

"Chronic quartan malaria nephropathy", well described over decades in the literature, mainly in areas endemic for *P. malariae*, causing "tropical nephrotic syndrome" or "quartan malaria nephrotic syndrome" in African children below the age of 10 years, was frequently reviewed in the past, but recently only sporadically reported from tropical Africa to the point, that it is currently questioned, whether it is truly associated with malaria infection at all (Barsoum, 1998; Barsoum, 2000; White, 2003a; Ehrich and Eke, 2007).

"Acute falciparum malaria nephropathy" - in contrast - was never questioned to be truly associated with malaria infection and is a well described complication and a major contributor to morbidity and mortality in *P. falciparum* infections (Habte, 1990; Eiam-Ong and Sitprija, 1998; Barsoum, 2000; Eiam-Ong, 2002). Infections with *P. vivax* or *P. ovale* are very rarely leading to ARF (White, 2003a; Ehrich and Eke, 2007).

Mild to moderate renal impairment, presenting with a raised level of serum creatinine, an elevation of blood urea nitrogen (BUN) and an increased BUN/Creatinine-ratio is a common finding in malaria (White, 2003a). Proteinuria and cylindruria with mild urinary sediment changes are also described in falciparum malaria in 20% to 60% of cases (Barsoum, 1998). These findings are usually transient and resolve spontaneously within a few days or weeks. In severe malaria however renal impairment can rapidly progress to renal failure if adequate rehydration or antimalarial treatment is delayed (Wilairatana et al., 1999). ARF may complicate around 30% of adult cases of severe malaria depending on endemicity (more common in areas of low or unstable-transmission), age, immune-status (more common in non-immune adults), delay of malaria treatment and other factors, but is rarely seen in children with severe malaria (Barsoum, 2000; Day et al., 2000b; White, 2003a). The ARF seen in *P. falciparum* infection usually presents 4 to 7 days after the onset of fever (Thuraisingham and Adu, 2007). Renal failure, as one WHO criterion for severe malaria, is defined by either, an urine output of less than 400 ml in 24 hours in adult patients and less than 0.5 ml per kg body-weight per hour in children, or a raised serum creatinine of more than 265 µmol/l (> 3,0 mg/dl) in adults and more than 130µmol/l (>1,5mg/dl) in children (WHO, 2006b). Both parameters are valid only, if prerenal failure due to volume depletion or hemodynamic instability is ruled out. Most cases of ARF in severe malaria are oliguric, hypercatabolic and associated with other complications (Barsoum, 2000): Jaundice, the most common association, is found in more than 75% cases of malarial associated renal failure (MARF)(Wilairatana et al., 1994).

The histological picture of MARF shows a variable mixture of acute tubular necrosis (ATN), acute (tubulo-) interstitial nephritis (AIN) postinfectious glomerulonephritis (PIGN) and mesangioproliferative glomerulonephritis (MPGN), with ATN being the most consistent histological finding (Barsoum, 2000). Complex interactions, including mechanical, immunological, inflammatory, cytokine-related and non-specific factors seem to be involved, but the exact causative mechanisms of MARF are still poorly understood (Elsheikha and Sheashaa, 2007).

A major contribution in the etiopathogenesis of MARF is attributed to prerenal conditions: Hemodynamic factors, including volume depletion, arterial hypotension and shock with alteration of renal perfusion, leading to renal vasoconstriction, consecutive parenchymal ischemia and ATN, seem to play a central role and – because of being the most accessible to treatment – have to be ruled out in any patient presenting with MARF (Ehrich and Eke, 2007). Besides hemodynamic factors "Cytoadherence" presenting with "Rosetting" (sticking of infected red blood cells to uninfected red blood cells) and "Sequestration" (attachment of infected red blood cells to the vascular endothelium) are well described phenomena in severe malaria, and obviously involved in many organ complications by leading to microvascular obstruction and tissue hypoxia (Leech et al., 1984; Chen et al., 2000; Miller et al., 2002; Eiam-Ong, 2002; Dondorp et al., 2004; Seydel et al., 2006). Sequestration of parasitized red blood cells, which is supposed to be the major feature in the pathophysiology of cerebral malaria, seems to be of minor importance in the pathology seen in the kidney, although cytoadherence of infected erythrocytes and monocytes has been described (Elsheikha and Sheashaa, 2007; Nguansangiam et al., 2007). A study comparing the relative proportion of schizonts to ring forms in the peripheral blood count (as an indicator for sequestration of infected red blood cells) showed, that sequestration is not the most arbitrative factor in MARF, explaining the observation, that MARF can be found both in patient with and without cerebral malaria (Nacher et al., 2001b). Besides the controversial demonstration and role of immune-complex depositions, immune-mediated endothelial damage leading to malarial nephritis, hyperparasitemia, haemolysis, hyperbilirubinaemia, intravascular coagulation, nitric oxide (NO) deregulation, cytokine activation and sepsis have been found to be contributing factors in the development of MARF (Clark and Cowden, 1999; Barsoum, 2000; Thuraisingham and Adu, 2007; Ehrich and Eke, 2007; Elsheikha and Sheashaa, 2007; Nguansangiam et al., 2007). Rhabdomyolysis has been described in MARF, but seems to be a rare cause (St John et al., 1995; Sinniah and Lye, 2000; Reynaud et al., 2005).

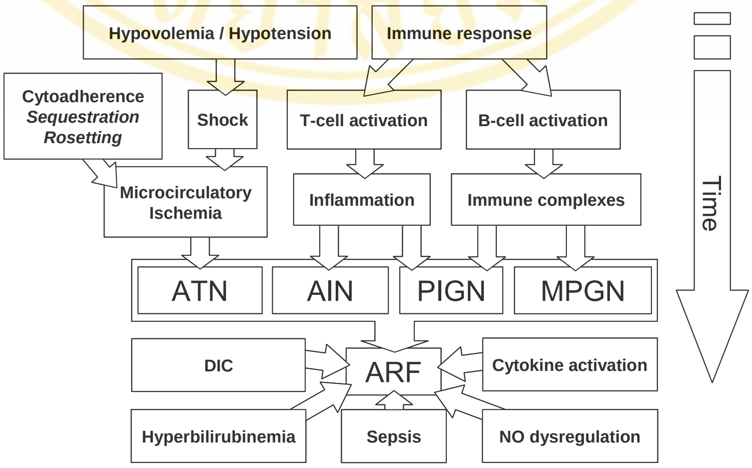


Figure 1: Proposed pathways of hemodynamic and immunologic factors in the pathogenesis of falciparum induced renal failure (Modified from Elshikha, Parasitol. Res. 2006 & Barsoum, J. Am. Soc. Nephrol. 2000).

"Blackwater fever", resulting from severe intravascular haemolysis and presenting with the passage of red to dark-brown or black urine due to extensive haemoglobinuria, may be associated with the development of MARF, although the majority of cases show a normal renal function (White, 2003a). The described mechanism of Blackwater renal failure is tubular necrosis (Bruneel et al., 2002). Three main risk factors and causative relations regarding the development of Blackwater fever have been identified:

1. Exposure of G6PD deficient patients to oxidant drugs (irrespective of whether malaria infection is present or not)
2. G6PD deficient malaria patients receiving quinine treatment (despite quinine being not an oxidant drug)
3. Some patients with quinine treated severe malaria despite normal G6PD-levels (White, 2003a)

Frequently observed in Europeans and Asians, working in colonial Africa at the beginning of the 20th century, Blackwater fever has become exceptional since 1950, when quinine was replaced by chloroquine. The disease reappeared in the 1990s, following the re-utilization of quinine because of the emerging chloroquine resistance (Bruneel et al., 2002; White, 2003a).

Late referral, acute onset of disease, severe anemia, significant jaundice, multiorgan involvement, hepatitis, acute respiratory distress, young age, sepsis and opportunistic pulmonary infections are all potential risk factors associated with higher mortality in MARF (Barsoum, 2000; Elsheikha and Sheashaa, 2007).

Not much is known about factors related to protection from MARF. One discussed factor is the interaction of helminth and malaria co-infection. Already 30 years ago Murray and colleagues reported, that infection with the intestinal nematode *Ascaris lumbricoides* was associated with the suppression of malaria symptoms and that anti-helminthic treatment can lead to malaria recrudescence (Murray et al., 1977; Murray et al., 1978). The interaction of helminth and malaria co-infection was intensively studied in the last years by Mathieu Nacher and colleagues, who found, that pre-existing helminth infections are associated with protection from MARF and cerebral malaria in adult Thai patients (Nacher et al., 2001a; Nacher et al., 2002). Nevertheless studies on the impact of helminth and malaria co-infection remain controversial: A case-control study in Senegal showed an increased risk of clinical malaria in children infected with soil-transmitted helminths compared to those uninfected (Spiegel et al., 2003). Another study conducted in Senegal reported, that children infected with *Ascaris lumbricoides* had an increased risk of severe malaria (Le Hesran et al., 2004). Despite controversial study results, differences in study population, location and design, the actual available data seems to support, that in its relationship to non-severe malaria, helminths are most likely to lead to an increased risk of disease while for severe malaria a reduction of risk among individuals infected with helminths can be assumed (Mwangi et al., 2006).

Early diagnosis, fast initiation of adequate anti-malaria treatment, and detection and proper treatment of haemodynamic prerenal conditions are the most important steps, to prevent the manifestation of MARF. If a patient remains oliguric despite adequate rehydration, and the creatinine- and BUN-levels are rising or already high, then fluids should be restricted to insensible-losses replacement only and the fluid intake and urine output needs careful monitoring (White, 2003a).

While dose restrictions in ARF are not necessary with the administration of Artemisinin derivatives, Quinine dosages should be reduced by one-third to one-half after 48 hours of treatment, to prevent the accumulation of toxic blood level concentrations in ARF (White, 2003a).

The role of loop-diuretics and catecholamines (especially the long-run propagated use of dopamine at "renal"-dose) in preventing progress from renal impairment to failure is controversial (White, 2003a). In a Vietnamese study on the effect of dopamine and epinephrine in severe malaria and severe sepsis results were disappointing: "Although dopamine increased and epinephrine decreased fractional renal blood flow, there was no evidence that either drug produced either a beneficial or a deleterious effect on renal oxygen metabolism or function at any of the doses investigated" (Day et al., 2000a).

If metabolic acidosis, uraemic complications, volume overload or hyperkalaemia is complicating renal failure, renal replacement therapy (RRT) is - if available - the only therapeutic option and needed in 50 to 90% of patients with MARF (different figures reported from different series and studies) (Wilairatana et al., 1999; Barsoum, 2000). Untreated ARF in adult patients has a case fatality rate of over 70% (Dondorp and Day, 2007). In a study carried out at a referral center for severe malaria cases in Vietnam it has been demonstrated, that the introduction of peritoneal dialysis can reduce the case fatality rate of MARF from 75% to 26% (Trang et al., 1992). If renal replacement therapy is performed, haemofiltration was shown to be superior to peritoneal dialysis in terms of mortality and cost-effectiveness (Phu et al., 2002). The limited efficiency of peritoneal dialysis in severe cases is, among other things, ascribed to the coexisting impaired splanchnic and peritoneal microcirculation (Wilairatana et al., 1999; White, 2003a). In a study conducted at the Bangkok Hospital for Tropical Diseases including 112 patients with MARF, 102 patients treated by haemodialysis had a case fatality rate of around 10% (Wilairatana et al., 1999). Data about the needed frequency and duration of haemodialysis in MARF is limited, but was reported to be around a median of 6.5 procedures (Range: 1 - 27) with a median duration of 9.7 days (Range: 1 - 41) in the Bangkok study (Wilairatana et al., 1999).

The major drawback of all forms of RRT is the limited availability and the associated high costs for the usually resource-poor countries in malaria endemic areas. If RRT is available, the crucial factor - with a very high impact on mortality - is the early referral, diagnosis and treatment of malaria before renal failure evolves: In the series of MARF treated with haemodialysis at the Bangkok Hospital for Tropical Diseases mentioned above, the majority of deaths occurred within 24 hours of starting haemodialysis or even before haemodialysis was started (Wilairatana et al., 1999).

Focusing on the fact, that MARF is often already present at admission and falciparum associated glomerulopathy is reversible, with lesions usually resolving within 2 to 6 weeks after eradication of infection and chronic renal failure as a very rarely seen complication, the major goal is to find prognostic factors to determine the necessity for early referral of the patient or starting RRT (Singhal et al., 1997; Elsheikha and Sheashaa, 2007).

CHAPTER III
OBJECTIVES

(1) To determine the case fatality rate in severe malaria patients with acute renal failure.

(2) To determine risk factors associated with death in patients with acute renal failure.

(3) To determine risk factors associated with dialysis in patients with acute renal failure.

(4) To determine risk factors associated with death in acute renal failure patients treated with dialysis.

CHAPTER IV
MATERIAL AND METHODS

Electronic resources

Table 2: Used electronic resources.

URL	Information obtained
http://www.ncbi.nlm.nih.gov	PubMed Database has been used for literature review
http://www.who.int/malaria/	Current epidemiological data on malaria and guidelines

Study site

The study was performed at Mae Sot General Hospital in Tak Province, located close to the Thai-Myanmar border in Thailand, an endemic area for vivax and falciparum malaria. Mae Sot General Hospital is a 317-bed hospital with a capacity of 20 intensive care beds (including 8 paediatric intensive care beds), admitting a number of around 20,800 in-patients and providing services to around 260,900 out-patients annually (hospital internal figures from 2005). Mae Sot General Hospital serves as referral hospital for complicated malaria cases in Mae Sot district and for four community hospitals in neighbouring districts. The Mae Sot district is a hypo-endemic, low-transmission area (approximately one infection per person per year), where asymptomatic malaria is unusual (Luxemburger et al., 1997). Malaria transmission is unstable and shows a seasonal pattern with two peaks between May and July and November and January (Paul et al., 1998). The present Plasmodium species found in the Mae Sot area are *P. falciparum* and *P. vivax*. The number of malaria cases - and the responsible Plasmodium species - treated at the Mae Sot General Hospital (In- and out-patients) in the past 13 years are shown below (Hospital internal figures):

Table 3: Number of malaria cases treated at Mae Sot General Hospital between 1994 and 2006.

Year	*1994*	*1995*	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	*2003*	*2004*	*2005*	*2006*
P.f.	3,902	2,086	1,462	1,111	1,278	1,331	1,216	894	569	439	284	520	1,056
P.v.	801	772	269	335	1,041	768	879	542	495	389	197	260	598
Total	4,703	2,858	1,731	1,446	2,319	2,099	2,095	1,436	1,064	828	481	780	1,654

Annotation to Table 3: The observed changes in the amount of malaria patients over the years is primarily reflecting changes in local referral politics, rather than changes in the local malaria-transmission or -incidence situation.

Study period

The time span, covered by this study, is a 6-years period from January 1st 2002 to December 31st 2007.

Data collection time

The data for this study were collected between November 2007 and January 2008.

Study population

The subjects included in this study are cases of malarial acute renal failure (as defined by the WHO-criteria for severe malaria 2006), admitted at Mae Sot General Hospital, Tak Province, Thailand from January 1st 2002 to December 31st 2007.

Due to the vicinity of the Thai-Myanmar border, the large number of ethnic Burmese living in Tak province, and the high percentage of Burmese workers in the agricultural and forest operation sector, Burmese (around 50% of all malaria cases in 2006) and ethnic Thai patients (around 49% of all malaria cases in 2006) share the biggest and fairly similar proportions of malaria infections treated at the Mae Sot

General Hospital. An almost negligible percentage (around 1% of all malaria cases in 2006) of local minorities ("hill-tribes"), namely Karen and Hmong, are treated for malaria at Mae Sot General Hospital (hospital internal figures).

Study design

This study was conducted as a descriptive observational retrospective study, to determine the case fatality rate of MARF (defined by the WHO-criteria for severe malaria 2006) and to evaluate clinical and paraclinical parameters as risk factors for death and for the need and outcome of RRT in MARF patients. The number of needed subjects were estimated by sample-size calculation (see below) and then planed to be retrospectively included by reviewing the medical records from the year 2007 backwards. The data were collected from medical records at Mae Sot General Hospital.

Inclusion criteria

(1) Patients with confirmed diagnosis of malaria by either: (A) the finding of asexual forms of malaria parasites in the blood by light microscopy or (B) a positive rapid diagnostic test, for the presence of malaria parasite antigen
(2) Malarial acute renal failure, defined by the WHO-criteria 2006

Exclusion criteria

(1) Pregnancy
(2) Patients with known history of pre-existing renal impairment or chronic kidney diseases
(3) Coexisting infections (leptospirosis, scrub typhus, etc.)

Sample-size calculation

For the sample-size calculation a case fatality rate of MARF cases of around 10% was assumed (according to a reported case fatality rate of 10.7% in a comparable setting- (with ICU and RRT facilities) and patient-profile at the Bangkok Hospital for Tropical Diseases (Wilairatana et al., 1999). With a desired degree of confidence of 95% - corresponding to an α-level of 0.05 - the critical value "z" was set at 1.96. The estimated case fatality rate of 10% set "p" = 0.1. The proportion of error "e" we were prepared to accept was set at 5% : e = 0.05. The estimated sample-size number "n" was therefore:

$$n = \frac{z^2 \times p(p-1)}{e^2} = 138$$

To determine whether the calculated sample-size would be a realistic reachable number, the yearly number of malaria associated ARF cases, admitted and treated at Mae Sot General Hospital over the last years has been obtained from the hospital internal records (Table 4):

Table 4: MARF cases at Mae Sot General Hospital from 2002 to 2006.

Year	2002	2003	2004	2005	2006	total
Cases of MARF	25	22	26	37	43	153

Data collection

After identifying eligible patients by using the hospital registry, the data - including demographic data, clinical and laboratory findings - of the cases fulfilling the inclusion criteria were extracted from the patients' files and recorded in the designed case record form (see appendix). Data were entered and stored in Microsoft Excel-files (Version 2002) before transformation into SPSS-files (Version 15.0 for Windows, Release 15.0.0, September 2006) for analysis.

Ethical approval

This study was reviewed and approved by the Ethical committee of the Faculty of Tropical Medicine of Mahidol University (Bangkok, Thailand).

Data analysis

The clinical and paraclinical parameters collected in this study were compared and summarized as means and standard deviations, then analysed by using t-test in case of normal distributed data, or summarized as medians and ranges and analysed by using Mann-Whitney U test in case of non-normal distributed data. For nominal data χ^2-test or Fisher's exact test was applied, as appropriate, and summarized as frequencies and percentages. Logistic regression was used to determine the different investigated clinical and paraclinical parameters as predictive risk factors for clinical outcome.

CHAPTER V
RESULTS

1. Recruitment of the studied MARF patients

By using the hospital's registry it was possible to identify a maximum number of 412 cases of severe malaria treated at Mae Sot General Hospital between January 1st 2002 and December 31st 2007. After obtaining the corresponding medical records and screening the files according to the inclusion and exclusion criteria, 76 cases finally fulfilled the criteria set for this study and were therefore included (Figure 2).

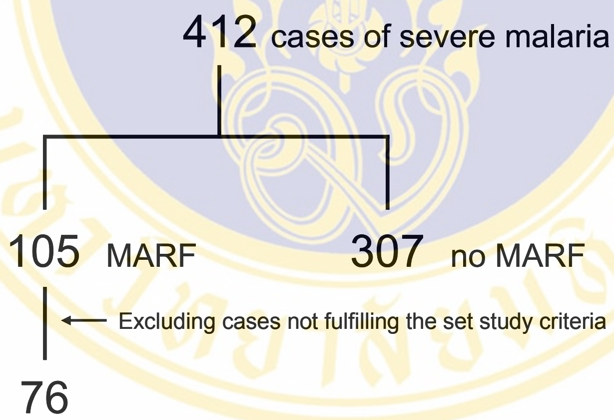


Figure 2: Flowchart for inclusion and exclusion of the studied MARF cases.

2. Seasonal pattern of MARF

Two seasonal peaks in MARF cases are observed among the 76 studied MARF cases. The first peak is found between May and August and the second is noticed between October and January (Figure 3).

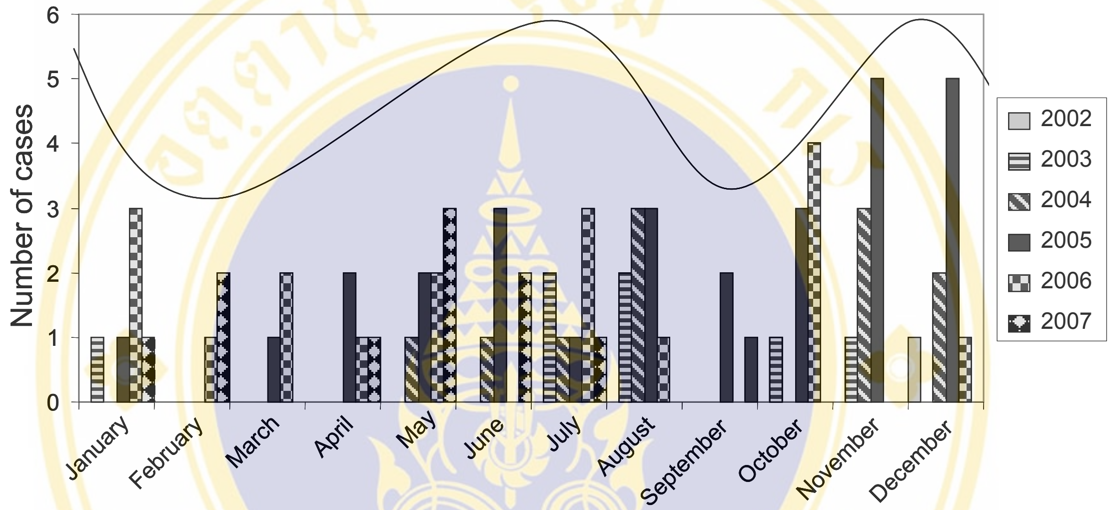


Figure 3: Seasonal pattern of MARF cases admitted at Mae Sot General Hospital over the years 2002 to 2007.

3. Demographical data

The observed age-distribution found among the 76 studied MARF cases shows a well defined peak among the working age-group with a median of 33.5 years and a wide range from the pre-school age of 4 years to the age of 74 years (Figure 4). The age distribution does not considerably differ between the two genders and the different ethnicities (Figure 5).

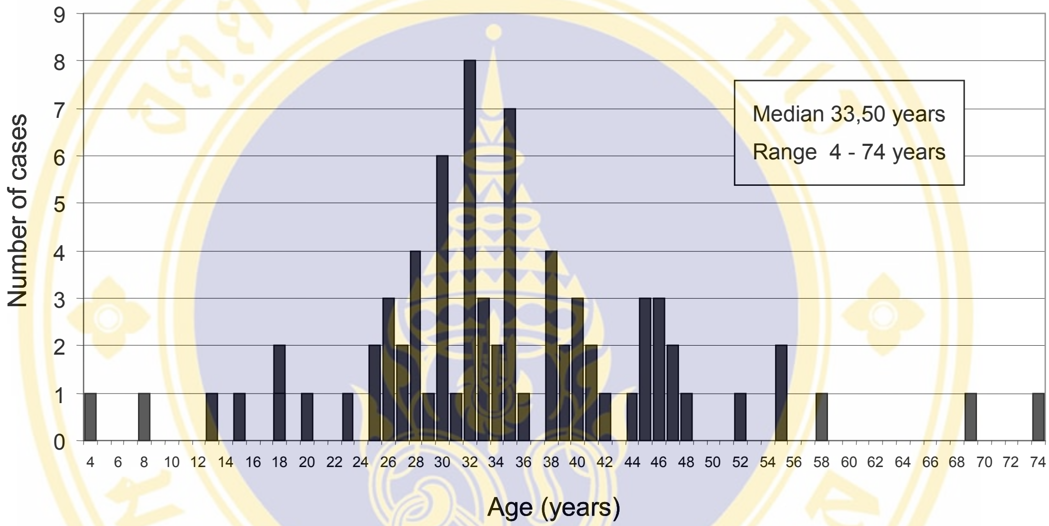
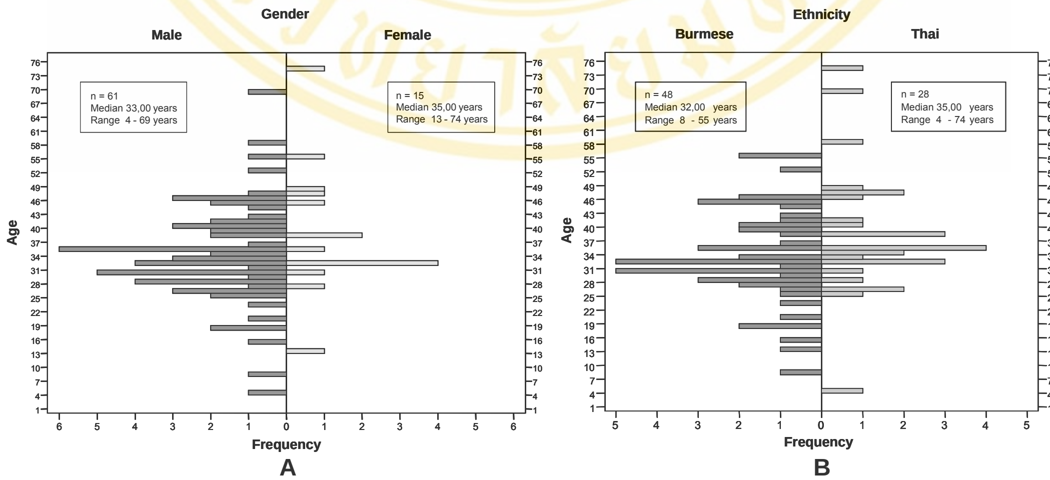


Figure 4: Age distribution of the 76 studied MARF cases.



(A) Mann-Whitney U test of male vs. female cases: p = 0.269

(B) Mann-Whitney U test of Burmese vs. Thai cases: p = 0.110

Figure 5: Gender (A) and ethnicity (B) related age distribution of the 76 studied MARF cases.

The demographic data reveals that despite most patients are residents of Mae Sot district or neighbouring districts quite a high percentage of Burmese residents is found among the studied cases. When it comes to ethnicity even the majority is found to be Burmese. The occupational groups present amongst our studied patients are exclusively "Labour" and "Farmer".

The available past medical history of the studied patients was only noted in 6 cases, most of them were Hepatitis B carrier.

The history of previous malaria infections was only obtainable from around a quarter of the patients with a positive history in 30% of the cases (Table 5).

Table 5: Demographic and baseline characteristics of the 76 studied cases.

Characteristics		Total number	n	%
Residency		76		
	Mae Sot district		31	40.8
	Other Tak district		25	32.9
	Burma		20	26.3
Ethnicity		76		
	Burmese		48	63.2
	Thai		28	36.8
Occupation		75		
	Labour		59	78.7
	Farmer		12	16.0
	None		4	5.3
Past medical history		6		
	HBs-Ag positive		4	66.6
	HBs-Ag positive & Epilepsy		1	16.7
	Gout arthritis		1	16.7
Malaria history		20		
	Yes		6	30.0
	No		14	70.0

4. Presenting symptoms prior to admission

Among the presenting symptoms prior to admission the three most commonly observed complaints are "Fever", some degree of "Alteration of consciousness" and "Chills" (Figure 6). Detailed frequency-distributions of the different symptoms related to the outcome survival and death and the need for RRT are shown in Table 6 and 7.

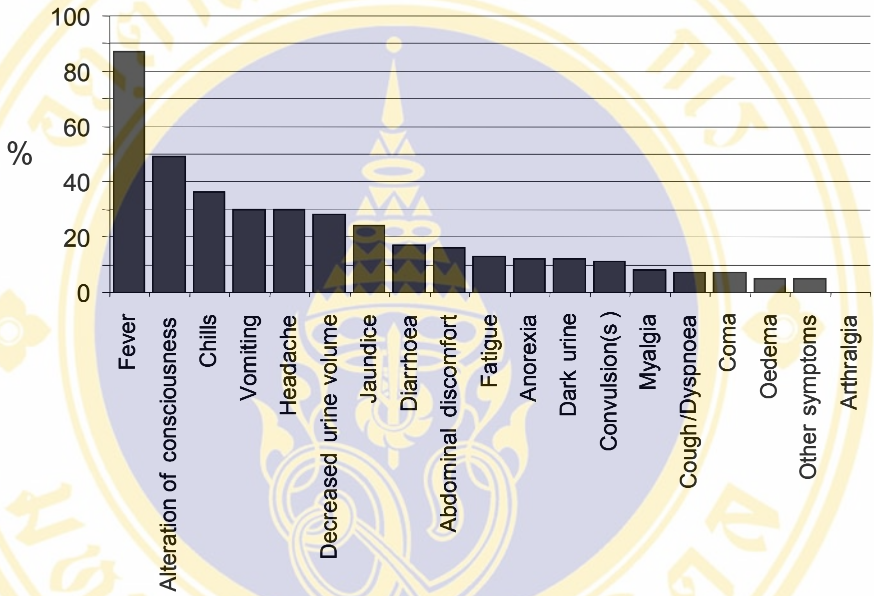


Figure 6: The frequency-distribution of the presenting symptoms prior to admission.

Table 6: The frequency-distribution of the symptoms prior to admission in relationship to death and survival.

Symptoms prior to admission	Total number of cases	Outcome			
		Survival		Death	
		n	%	n	%
Fever	66	49	74.2	17	25.8
Alteration of consciousness	37	22	59.5	15	40.5
Chills	27	19	70.4	8	29.6
Vomiting	23	17	73.9	6	26.1
Headache	23	19	82.6	4	17.4
Decreased urine volume	21	16	76.2	5	23.8
Jaundice	18	12	66.7	6	33.3
Diarrhoea	13	9	69.2	4	30.8
Abdominal discomfort	12	10	83.3	2	16.7
Fatigue	10	9	90.0	1	10.0
Anorexia	9	7	77.8	2	22.2
Dark urine	9	6	66.7	3	33.3
Convulsion(s)	8	4	50.0	4	50.0
Myalgia	6	6	100	0	0
Cough / Dyspnoea	5	3	60.0	2	40.0
Coma	5	1	20.0	4	80.0
Oedema	4	4	-	0	-
Other symptoms	4	4	-	0	-
Melena	2	2	-	0	-
Haematochezia	1	1	-	0	-
Epistaxis	1	1	-	0	-

Table 7: The frequency-distribution of the symptoms prior to admission in relationship to the use of RRT.

Symptoms prior to admission	Total number of cases	Outcome			
		No RRT		RRT	
		n	%	n	%
Fever	66	36	54.5	30	45.5
Alteration of consciousness	37	16	43.2	21	56.8
Chills	27	13	48.1	14	51.9
Vomiting	23	16	69.6	7	30.4
Headache	23	15	65.2	8	34.8
Decreased urine volume	21	10	47.6	11	52.4
Jaundice	18	8	44.4	10	55.6
Diarrhoea	13	8	61.5	5	38.5
Abdominal discomfort	12	6	50.0	6	50.0
Fatigue	10	5	50.0	5	50.0
Anorexia	9	7	77.8	2	22.2
Dark urine	9	5	55.6	4	44.4
Convulsion(s)	8	5	62.5	3	37.5
Myalgia	6	4	66.7	2	33.3
Cough / Dyspnoea	5	4	80.0	1	20.0
Coma	5	3	60.0	2	40.0
Oedema	4	3	-	1	-
Other symptoms	4	4	-	0	-
Melena	2	2	-	0	-
Haematochezia	1	1	-	0	-
Epistaxis	1	1	-	0	-

To evaluate the impact of delayed treatment in MARF, the time span between the onset of the first malaria related symptoms and hospital admission was reconstructed from the patients' files and afterwards analysed for statistically significant relationships to the outcome survival and death and the need for RRT. The observed median (range) time span between the onset of the first malaria related symptoms and the admission at Mae Sot General Hospital was 4 days (1 - 10 days) (Figure 7). When analysed for a putative relationship to the outcome survival and death and the need for RRT, no statistically significant difference is found (Table 8 and 9).

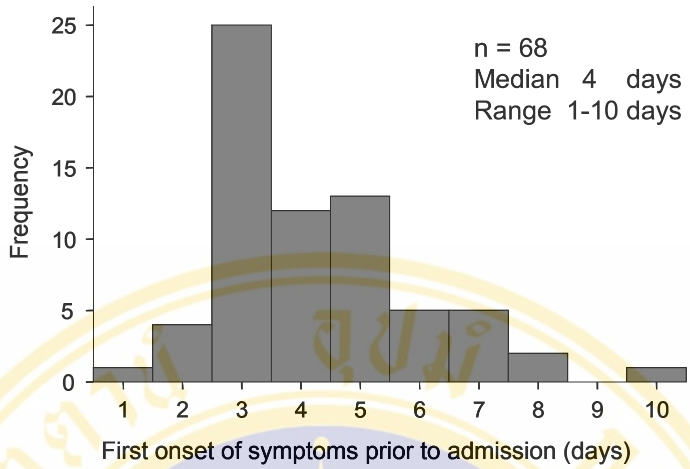


Figure 7: First onset of symptoms in days prior to admission.

Table 8: First onset of symptoms prior to admission in relationship to survival and death.

First onset of symptoms prior to admission (days prior to admission)	Total number of cases	Outcome				p-value
		Survival		Death		
		n	%	n	%	
≤ 4 days	42	31	73.8	11	26.2	0.773
> 4 days	26	20	76.9	6	23.1	
≤ 3 days	30	23	76.7	7	23.3	0.778
> 3 days	38	28	73.6	10	26.3	
1-3 days	30	23	76.7	7	23.3	-
4-6 days	30	23	76.7	7	23.3	
≥ 7 days	8	5	62.5	3	37.5	
1-6 days	60	46	76.7	14	23.2	0.402 *
≥ 7 days	8	5	62.5	3	37.5	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 9: First onset of symptoms prior to admission in relationship to the use of RRT.

First onset of symptoms prior to admission (days prior to admission)	Total number of cases	Outcome				p-value
		No RRT		RRT		
		n	%	n	%	
≤ 4 days	42	21	50.0	21	50.0	0.214
> 4 days	26	17	65.4	9	34.6	
≤ 3 days	30	17	56.7	13	43.4	0.908
> 3 days	38	21	55.3	17	44.7	
1-3 days	30	17	56.7	13	43.3	-
4-6 days	30	17	56.7	13	43.3	
≥ 7 days	8	4	50.0	4	50.0	
1-6 days	60	34	56.7	26	43.3	0.724 *
≥ 7 days	8	4	50.0	4	50.0	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

5. Case fatality rate / Outcome of MARF cases at Mae Sot General Hospital

Fatal cases are found in all age-groups among the studied 76 MARF patients (Figure 8). To evaluate putative age-, gender- and ethnicity-related mortality risks and possible outcome differences of referred versa direct admitted MARF cases corresponding subgroup analysis has been carried out (Table 10, 11, 12 and 13). While neither age nor gender, ethnicity or differences in treatment delay between the different ethnical groups showed any statistically significant relevance in relationship to the different outcomes (Table 10, 11 and 12), a statistically significant higher case fatality rate was found in the group of referred cases when compared to directly admitted cases (p = 0.037)(Table 13). Further subgroup analysis showed a statistically significant higher case fatality rate among cases being referred from Mae-Tao-Clinic and MSF (p = 0.009)(Table 13).

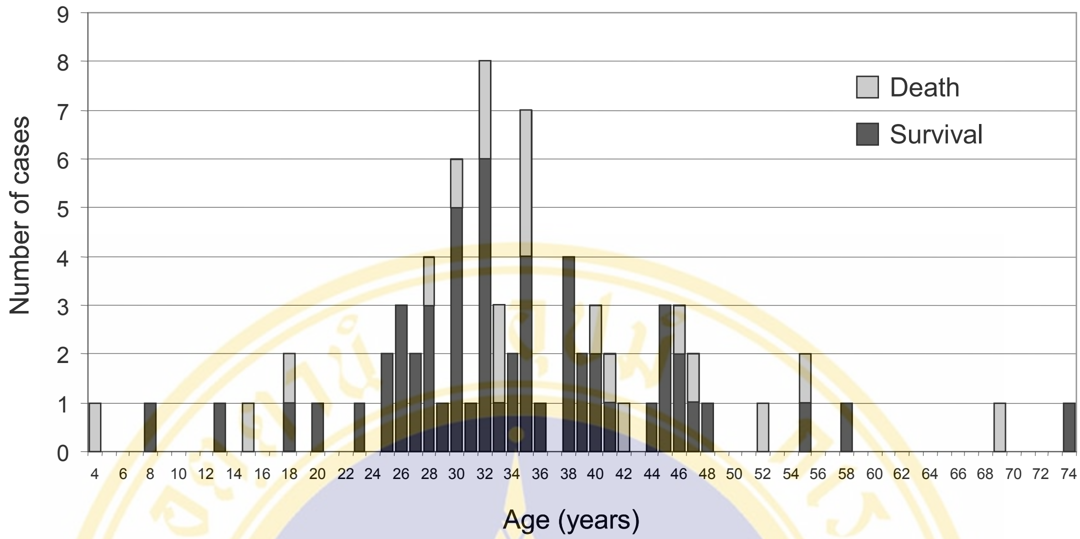


Figure 8: Distribution of survival and death among the 76 studied MARF cases.

Table 10: Age related outcome.

Age related outcome	Age (years)	Total number of cases	Outcome				p-value
			Survival		Death		
			n	%	n	%	
Age-groups	≤14	3	2	66.7	1	33.3	-
	15-34	37	29	78.4	8	21.6	-
	35-54	31	22	71.0	9	29.0	-
	≥55	5	3	60.0	2	40.0	-
Age-groups	≤40	57	44	77.2	13	22.8	0.229
	>40	19	12	63.2	7	36.8	
Total		76	56	73.7	20	26.3	

Table 11: Gender and ethnicity related outcome.

Gender and ethnicity related outcome		Total number of cases	Outcome				p-value
			Survival		Death		
			n	%	n	%	
Gender		76					
	Male	61	45	73.8	16	26.2	1.000 *
	Female	15	11	73.3	4	26.7	
Ethnicity		76					
	Burmese	48	34	70.8	14	29.2	0.460
	Thai	28	22	78.6	6	21.4	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 12: First onset of symptoms prior to admission in relationship to ethnicity.

First onset of symptoms prior to admission (days prior to admission)	Total number of cases	Ethnicity				p-value
		Burmese		Thai		
		n	%	n	%	
≤ 4 days	42	26	61.9	16	38.1	0.976
> 4 days	26	16	61.5	10	38.5	
≤ 3 days	30	17	56.7	13	43.3	0.442
> 3 days	38	25	65.8	13	34.2	
1-3 days	30	17	56.7	13	43.3	-
4-6 days	30	21	70.0	9	30.0	
≥ 7 days	8	4	50.0	4	50.0	
1-6 days	60	38	63.3	22	36.7	0.470
≥ 7 days	8	4	50.0	4	50.0	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 13: Outcome of the directly admitted vs. referred MARF cases.

Outcome of directly admitted vs. referred cases	Number of cases	%	Outcome: Survival n	Survival %	Death n	Death %	p-value
Direct admission & Malaria clinic referral	38	50.0	32	84.2	6	15.8	
Referral	38	50.0	24	63.2	14	36.8	0.037 *
Community hospital	22	57.9	16	72.7	6	27.3	0.284 †
Mae-Tao-Clinic & MSF#	16	42.1	8	50.0	8	50.0	0.009 ‡
Total	76	100	56	73.7	20	26.3	0.033 §

(#MSF = Médecins Sans frontières)

§ Chi-Square test of "Direct admission & Malaria clinic referrals" vs. "Community hospital referrals" vs. "Mae-Tao-Clinic & MSF referrals": p-value = 0.033

* Chi-Square test of "Direct admission & Malaria clinic referrals" vs. "Referrals": p-value = 0.037

† Chi-Square test of "Direct admission & Malaria clinic referrals" vs. "Community hospital referrals": p-value = 0.284

‡ Chi-Square test of "Direct admission & Malaria clinic referrals" vs. "Mae-Tao-Clinic & MSF referrals": p-value = 0.009

To determine the range of time spans and a possible pattern between admission time and death in the fatal MARF cases, the exact length of each patient's hospitalisation has been evaluated (Figure 9). With a median of 44:42 [h:min] (ranging from 1:30 [h:min] to 660:19 [h:min]) more than half of the fatal MARF cases (55%) died within 48 hours after admission.

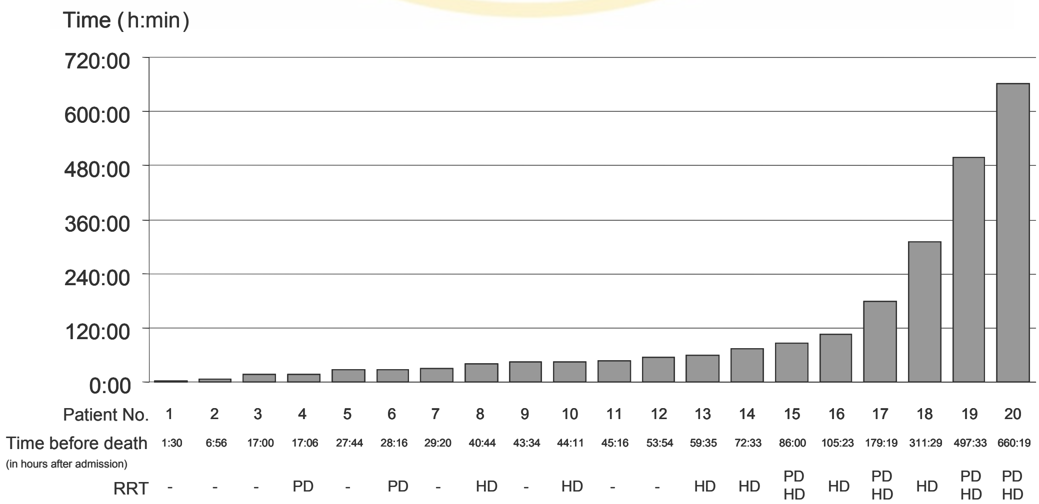


Figure 9: Hours before death after admission in the fatal MARF cases.

6. Analysis of clinical symptoms, therapeutical interventions, complications and laboratory parameters as putative risk factors for death, the need for RRT and the outcome of RRT

To evaluate the presenting symptoms at the time of the patient's admission, the renal failure classification and the needed therapeutical interventions as predictive risk factors for survival and death, the need for RRT and the outcome of RRT the individual parameters have been analysed accordingly (Table 14, 15, 16, 17 and 18).

Among the presenting symptoms at the time of admission the presence of an "Impaired consciousness" ($p < 0.001$), a "GCS < 10" ($p = 0.002$), "Hepatomegaly" ($p = 0.009$) and "Coma" ($p = 0.012$) showed a significant association with death (Table 14), while an "Impaired consciousness" ($p < 0.001$) and a "GCS < 10" ($p = 0.018$) showed a significant association with the need for RRT (Table 15).

Among the analysed therapeutical interventions showing a relationship to survival and death, the use of "Mechanical ventilation", the need for "Inotropic drugs" and the "Transfusion of FFP" (Fresh frozen plasma) are significant associated (Table 16). Although not statistically significant the need for RRT shows a statistically tendency toward a higher frequency of a fatal outcome (Table 16.)

When cross-tabulated for the need of RRT, patients presenting with "Anuria / Oliguria" ($p = 0.001$), a "Hypercatabolic state" ($p < 0,001$), the need for "Mechanical ventilation" ($p < 0.001$) and "Inotropic drugs" ($p < 0.001$) as well as "Transfusion of blood products" ($p = 0.004$) are significant more frequently found among dialysed patients (Table 17). Among the different transfused blood products RBC (Red blood cells) ($p = 0.034$) as well as FFP ($p = 0.016$) showed individually significant associations with the need for RRT (Table 17).

Fatal cases among patients receiving RRT were found to be associated with the need for "Mechanical ventilation" ($p < 0.001$), "Inotropic drugs" ($p < 0.001$) and "Transfusion of FFP" ($p = 0.008$) (Table 18).

53 of the 76 studied cases (69.7%) received blood component transfusions: 49 (64.5%) received RBC, 20 (26.3%) received FFP and 16 (21.1%) received both (Table 16). The median amount of transfused RBC volume was 590 ml (230 - 1760 ml). The median amount of transfuse FFP volume was 780 ml (280 - 2346 ml).

Table 14: The frequency-distribution of the presenting symptoms at the time of admission in relationship to survival and death.

Presenting symptom at the time of admission	Total number of cases	Outcome				p-value
		Survival		Death		
		n	%	n	%	
Jaundice	70					
No	27	19	70.4	8	29.6	0.553
Yes	43	33	76.7	10	23.3	
Impaired consciousness	71					
No	30	28	93.3	2	6.7	< 0.001 *
Yes	41	23	56.1	18	43.9	
GCS ≤ 10	52					
No	36	29	80.6	7	19.4	0.002
Yes	16	6	37.5	10	62.5	
Anemia	69					
No	31	26	83.9	5	16.1	0.055
Yes	38	24	63.2	14	36.8	
Hepatomegaly	68					
No	44	38	86.4	6	13.6	0.009
Yes	24	14	58.3	10	41.7	
Coma	72					
No	65	51	78.5	14	21.5	0.012 *
Yes	7	2	28.6	5	71.4	
Splenomegaly	67					
No	62	50	80.6	12	19.4	0.070 *
Yes	5	2	40.0	3	60.0	
Convulsions	72					
No	69	51	73.9	18	26.1	-
Yes	3	1	33.3	2	66.7	
Oedema	55					
No	53	41	77.4	12	22.6	-
Yes	2	1	50.0	1	50.0	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 15: The frequency-distribution of the presenting symptoms at the time of admission in relationship to the use of RRT.

Presenting symptom at the time of admission	Total number of cases	Outcome				p-value
		No RRT		RRT		
		n	%	n	%	
Jaundice	70					
No	27	18	66.7	9	33.3	0.202
Yes	43	22	51.2	21	48.8	
Impaired consciousness	71					
No	30	25	83.3	5	16.7	< 0.001
Yes	41	14	34.1	27	65.9	
GCS ≤ 10	52					
No	36	24	66.7	12	33.3	0.018
Yes	16	5	31.3	11	68.7	
Anemia	69					
No	31	19	61.3	12	38.7	0.614
Yes	38	21	55.3	17	44.7	
Hepatomegaly	68					
No	44	29	65.9	15	34.1	0.341
Yes	24	13	54.2	11	45.8	
Coma	72					
No	65	38	58.5	27	41.5	0.230 *
Yes	7	2	28.6	5	71.4	
Splenomegaly	67					
No	62	39	62.9	23	37.1	0.897 *
Yes	5	3	60.0	2	40.0	
Convulsions	72					
No	69	39	56.5	30	43.5	0.581 *
Yes	3	1	33.3	2	66.7	
Oedema	55					
No	53	31	58.5	22	41.5	0.186 *
Yes	2	0	0	2	100	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 16: Renal failure classification and therapeutical interventions in relationship to survival and death.

Renal failure classification / Therapeutical intervention	Total number of cases		Outcome				p-value
			Survival		Death		
	n	%	n	%	n	%	
Renal failure	76						
Present at admission	69	90.8	51	73.9	18	26.1	0.887
Developing after admission	7	9.2	5	71.4	2	28.6	
Renal failure classification	63						
Anuric	4	6.3	2	50.0	2	50.0	
Oliguric	33	52.4	24	72.7	9	27.3	
Non-oliguric	26	41.3	20	76.9	6	23.1	0.558 *
Hypercatabolic state	58						
No	19	32.8	17	89.5	2	10.5	0.302 §
Yes	39	67.2	29	74.4	10	25.6	
Renal replacement therapy	76						
No	44	57.9	36	81.8	8	18.2	0.059
Yes	32	42.1	20	62.5	12	37.5	
Peritoneal dialysis (PD)	10	13.2	8	80	2	20	
Haemodialysis (HD)	16	21.0	10	62.5	6	37.5	
PD + HD	6	7.9	2	33.3	4	66.7	
Mechanical ventilation	76						
No	46	60.5	45	97.8	1	2.2	< 0.001
Yes	30	39.5	11	36.7	19	63.3	
Inotropic drugs	76						
No	48	63.2	46	95.8	2	4.2	< 0.001
Yes	28	36.8	10	35.7	18	64.3	
Transfusion of blood products	76						
No	23	30.3	19	82.6	4	17.4	
Yes	53	69.7	37	69.8	16	30.2	0.244 §
RBC	49	64.5	35	71.4	14	28.6	0.547 §
FFP	20	26.3	10	50.0	10	50.0	0.008 §

* Chi-square test for the pooled oliguric and anuric RF cases vs. the non-oliguric RF cases: p = 0,558

§ In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 17: Renal failure classification and therapeutical interventions in relationship to the use of RRT.

Renal failure classification / Therapeutical intervention	Total number of cases		Outcome				p-value
			No RRT		RRT		
	n	%	n	%	n	%	
Renal failure	76						
Present at admission	69	90.8	39	56.5	30	43.5	0.692 §
Developing after admission	7	9.2	5	71.4	2	28.6	
Renal failure classification	63						
Anuric	4	6.3	0	0	4	100	0.113 †
Oliguric	33	52.4	12	36.4	21	63.6	
Non-oliguric	26	41.3	19	73.1	7	26.9	0.001 *
Hypercatabolic state	58						
No	19	32.8	19	100	0	0	< 0.001 §
Yes	39	67.2	14	35.9	25	64.1	
Mechanical ventilation	76	100					
No	46	60.5	34	73.9	12	26.1	< 0.001
Yes	30	39.5	10	33.3	20	66.7	
Inotropic drugs	76	100					
No	48	63.2	36	75	12	25	< 0.001
Yes	28	36.8	8	28.6	20	71.4	
Transfusion of blood products	76	100					
No	23	30.3	19	82.6	4	17.4	0.004 §
Yes	53	69.7	25	47.2	28	52.8	
RBC	49		24	49.0	25	51.0	0.034 §
FFP	20		7	35.0	13	65.0	0.016 §

* Chi-square test for the pooled anuric and oliguric RF cases vs. the non-oliguric RF cases: p = 0.001

† Fisher's exact test for the anuric RF cases vs. the pooled oliguric & non-oliguric RF cases: p = 0.113

§ In the cases of a number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 18: Renal failure classification and therapeutical interventions in relationship to survival and death in RRT.

Renal failure classification / Therapeutical intervention	Total number of cases		Outcome				p-value
			RRT - Survival		RRT - Death		
	n	%	n	%	n	%	
Renal failure	32						
Present at admission	30	93.8	20	66.7	10	33.3	0.133 *
Developing after admission	2	6.2	0	0	2	100	
Renal failure classification	32						
Anuric	4	12.5	2	50.0	2	50.0	
Oliguric	21	65.6	14	66.7	7	33.3	
Non-oliguric	7	21.9	4	57.1	3	42.9	1.000 *
Hypercatabolic state	25						
No	0	0	0	0	0	0	-
Yes	25	100	17	68.0	8	32.0	
Renal replacement therapy	32						
Peritoneal dialysis (PD)	10	31.3	8	80.0	2	20.0	-
Haemodialysis (HD)	16	50.0	10	62.5	6	37.5	-
PD + HD	6	18.7	2	33.3	4	66.7	-
Mechanical ventilation	32						
No	12	37.5	12	100	0	0	0.001 *
Yes	20	62.5	8	40.0	12	60.0	
Inotropic drugs	32						
No	12	37.5	12	100	0	0	0.001 *
Yes	20	62.5	8	40.0	12	60.0	
Transfusion of blood products	32						
No	7	21.9	4	57.1	3	42.9	1.000 *
Yes	25	78.1	16	64.0	9	36.0	
RBC	25	100	16	64.0	9	36.0	1.000 *
FFP	13	52.0	5	38.5	8	61.5	0.020

§ Chi-square test for the pooled oliguric and anuric RF cases vs. the non-oliguric RF cases: p = 1.000

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

In order to assess the pattern of the most frequently identified RRT-indications in MARF patients, a frequency-distribution of the different complications present at the time of RRT initiation has been analysed. Among the 32 studied MARF cases treated with dialysis, the most prominent and equally frequent observed complications were "Anuria / Oliguria", "Acidosis" and a "Hypercatabolic state", present in 25 cases (78%) each. Pulmonary oedema indicating fluid overload was present in 11 cases (34%). Hyperkalaemia was present in 9 cases (28%). As exactly same numbers of cases with "Anuria / Oliguria", "Acidosis" and a "Hypercatabolic state" were found among the dialysed cases - raising the suspicion, whether these might be identical patients - a subgroup analysis has been performed: The subgroup analysis showed that 21 of the 25 patients with "Anuria / Oliguria" had a concomitant "Hypercatabolic state", 19 of the 25 patients with "Anuria / Oliguria" had concomitant "Acidosis", 18 patients with "Acidosis" also presented a "Hypercatabolic state" and 15 patients showed all three complications (Figure 10).

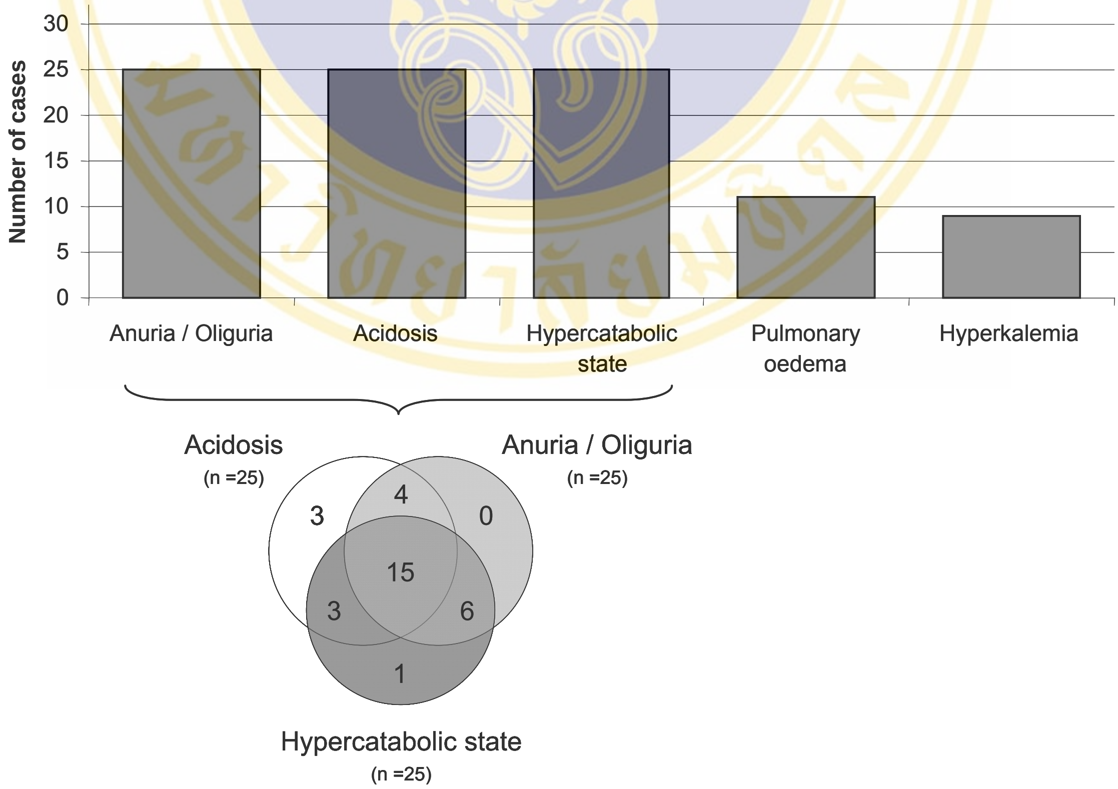


Figure 10: Complications present at the time of RRT initiation.

To investigate the usage of FFP transfusions as method to counterbalance circulatory collapse, the frequency of FFP transfusions has been cross-tabulated to the frequency of circulatory collapse / inotropic drugs. A significant association between these groups was found ($p < 0.001$) (Table 19).

Table 19: The relationship between FFP transfusions and circulatory collapse indicated by the use of inotropic drugs.

FFP transfusion and circulatory collapse / Inotropic drug use	Total number of cases	Outcome				p-value
		No circulatory collapse / No inotropic drugs		Circulatory failure / Inotropic drugs		
		n	%	n	%	
FFP transfusion	76					
No	56	44	78.6	12	21.4	< 0.001 *
Yes	20	4	20.0	16	80.0	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

As FFP transfusions are regarded as a risk factor for the development of ARDS an analytic cross-tabulation has been performed accordingly. Even though FFP transfusions are more frequently found among patients diagnosed with "ARDS / Pulmonary oedema", no statistically significance is observed (Table 20).

Table 20: The relationship between FFP transfusions and the incidence of ARDS / Pulmonary oedema.

FFP and ARDS / Pulmonary oedema	Total number of cases	Outcome				p-value
		No ARDS / Pulmonary oedema		ARDS / Pulmonary oedema		
		n	%	n	%	
FFP transfusion	74					
No	55	45	81.8	10	18.2	0.096
Yes	19	12	63.2	7	36.8	

With MARF mostly being described as "Oliguric and Hypercatabolic" in nature, further analysis has been performed focusing on the link between the need for intensive medical care and the presence of a hypercatabolic metabolic situation: The "Urine output" ($p = 0.042$) as well as the need for "Mechanical ventilation" ($p = 0.008$) and "Inotropic drugs" ($p = 0.008$) showed significant associations with a hypercatabolic metabolic state (Table 21).

Table 21: The hypercatabolic state related to urine-output and therapeutical interventions.

Hypercatabolic state		Total number of cases		Hypercatabolic state: No		Hypercatabolic state: Yes		p-value
		n	%	n	%	n	%	
Urine output		52						
	Anuria	2	3.8	0	0	2	100	
	Oliguria	30	57.7	6	20.0	24	80.0	0.042 †
	Non-oliguria	20	38.5	9	45.0	11	55.0	
Mechanical ventilation		58						
	No	37	63.8	17	46.0	20	54.0	0.008 *
	Yes	21	36.2	2	9.5	19	90.5	
Inotropic drugs		58						
	No	37	63.8	17	46.0	20	54.0	0.008 *
	Yes	21	36.2	2	9.5	19	90.5	

† Chi-Square test for the pooled anuric & oliguric RF cases vs. the non-oliguric RF cases: p-value= 0.042

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Severe malaria is frequently presenting with multi-organ involvement. To assess the pattern and frequency-distribution of the different organ-system involvements in the studied MARF cases, the patients' laboratory data and file-notes were screened for the presence of the WHO-criteria for severe malaria at any point during the patients' hospitalisation (WHO, 2006b). Figure 11 shows the frequency-distribution of the different complications presenting at admission or developing during hospitalisation among the investigated MARF cases. Note that the WHO-criteria "Hyperparasitemia" and "Haemoglobinuria" are, due to the lack of data, absent in the presented table.

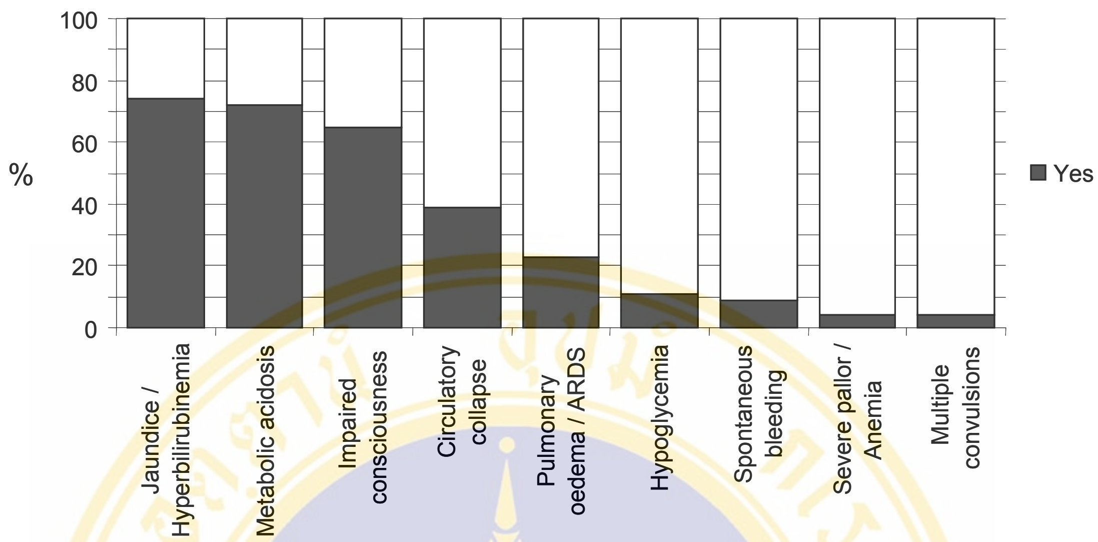


Figure 11: The frequency-distribution of the WHO-criteria for severe malaria found among the studied MARF cases.

To determine the value of the WHO-criteria as putative predictive factors for the outcome survival and death, the need for RRT and the outcome of RRT in MARF patients, the different criteria were individually analysed:

The factors "Metabolic acidosis" ($p = 0.015$), "Impaired consciousness"($p = 0.006$), "GCS < 10" ($p = 0.002$) and "Circulatory collapse" ($p < 0.001$) showed an independent significant association with death (Table 22) while an "Impaired consciousness" ($p = 0.002$), a "GCS < 10" ($p = 0.018$), the presence of "Circulatory collapse" ($p < 0.001$) and/or "Pulmonary oedema / ARDS" ($p = 0.042$) were significant associated with the need for RRT (Table 23) and "Metabolic acidosis" ($p = 0.029$), "Impaired consciousness" ($p = 0.045$), a "GCS < 10" ($p < 0.001$), "Circulatory collapse" ($p = 0.001$) and "Pulmonary oedema / ARDS" ($p = 0.029$) were significant more often found among dialysed patients with a fatal outcome (Table 24).

Table 22: The frequency-distribution of the WHO-criteria for severe malaria in relationship to survival and death.

WHO-criteria for severe malaria	Total number of cases	Outcome				p-value
		Survival		Death		
		n	%	n	%	
Jaundice / Hyperbilirubinaemia	74					
No	19	14	73.7	5	26.3	0.941
Yes	55	41	74.5	14	25.5	
Metabolic acidosis	72					
No	20	19	95.0	1	5.0	0.015 *
Yes	52	34	65.4	18	34.6	
Impaired consciousness	74					
No	26	24	92.3	2	7.7	0.006 *
Yes	48	30	62.5	18	37.5	
GCS ≤ 10	52					
No	36	29	80.6	7	19.4	0.002
Yes	16	6	37.5	10	62.5	
Circulatory collapse	76					
No	46	44	95.7	2	4.3	< 0.001 *
Yes	30	12	40.0	18	60.0	
Pulmonary oedema / ARDS	74					
No	57	46	80.7	11	19.3	0.065
Yes	17	10	58.8	7	41.2	
Hypoglycemia	76					
No	68	52	76.5	16	23.5	0.196 *
Yes	8	4	50.0	4	50.0	
Spontaneous bleeding	76					
No	69	52	75.4	17	24.6	0.371 *
Yes	7	4	57.1	3	42.9	
Severe pallor / Anemia	76					
No	73	55	75.3	18	24.7	-
Yes	3	1	33.3	2	66.7	
Multiple convulsions	75					
No	72	54	75.0	18	25.0	-
Yes	3	1	73.3	2	26.7	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 23: The frequency-distribution of the WHO-criteria for severe malaria in relationship to the use of RRT.

WHO-critereia for severe malaria	Total number of cases	Outcome				p-value
		No RRT		RRT		
		n	%	n	%	
Jaundice / Hyperbilirubinaemia	74					
No	19	14	73.7	5	26.3	0.110
Yes	55	29	52.7	26	47.3	
Metabolic acidosis	72					
No	20	13	65.0	7	35.0	0.317
Yes	52	27	51.9	25	48.1	
Impaired consciousness	74					
No	26	21	80.8	5	19.2	0.002
Yes	48	21	43.8	27	56.2	
GCS ≤ 10	52					
No	36	24	66.7	12	33.3	0.018
Yes	16	5	31.3	11	68.7	
Circulatory collapse	76					
No	46	34	73.9	12	26.1	< 0.001
Yes	30	10	33.3	20	66.7	
Pulmonary oedema / ARDS	74					
No	57	36	63.2	21	36.8	0.042
Yes	17	6	35.3	11	64.7	
Hypoglycemia	76					
No	68	41	60.3	27	39.7	0.217 *
Yes	8	3	37.5	5	62.5	
Spontaneous bleeding	76					
No	69	39	56.5	30	43.5	0.447 *
Yes	7	5	71.4	2	28.6	
Severe pallor / Anemia	76					
No	73	42	57.5	31	42.5	
Yes	3	2	66.7	1	33.3	-
Multiple convulsions	75					
No	72	41	56.9	31	43.1	
Yes	3	2	66.7	1	33.3	-

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

Table 24: The frequency-distribution of the WHO-criteria in relationship to survival and death in RRT.

WHO-criteria for severe malaria	Total number of cases	Outcome				p-value
		RRT - Survival		RRT - Death		
		n	%	n	%	
Jaundice / Hyperbilirubinaemia	31					
No	5	3	60.0	2	40.0	1.000 *
Yes	26	17	65.4	9	34.6	
Metabolic acidosis	32					
No	7	7	100	0	0	0.029 *
Yes	25	13	52.0	12	48.0	
Impaired consciousness	32					
No	5	4	80.0	1	20.0	0.045 *
Yes	27	16	59.3	11	40.7	
GCS ≤ 10	23					
No	12	7	58.3	5	41.7	< 0.0001
Yes	11	5	45.5	6	54.5	
Circulatory collapse	32					
No	12	12	100	0	0	0.001 *
Yes	20	8	40.0	12	60.0	
Pulmonary oedema / ARDS	32					
No	21	13	61.9	8	38.1	0.029 *
Yes	11	7	63.6	4	36.4	
Hypoglycemia	23					
No	18	10	55.6	8	44.4	1.000 *
Yes	5	2	40.0	3	60.0	
Spontaneous bleeding	32					
No	30	19	63.3	11	36.7	-
Yes	2	1	50.0	1	50.0	
Severe pallor / Anemia	32					
No	31	19	61.3	12	38.7	-
Yes	1	1	100	0	0	
Multiple convulsions	32					
No	31	20	64.5	11	35.5	-
Yes	1	0	0	1	100	

* In the cases of an expected number less than 5 in a subgroup, Fisher's exact test replaced the otherwise used Pearson Chi-square test.

To determine the value of the different paraclinical parameters as putative predictive factors for the outcome survival and death, the need for RRT and the outcome of RRT in MARF patients, the different laboratory parameters were individually analysed.

Among the analysed parameters fatal MARF cases showed significant higher "WBC" (White blood cell) counts ($p < 0.001$), lower "HCO_3^-" levels ($p = 0.001$), higher "AST" levels ($p = 0.001$), higher "ALT" levels ($p = 0.015$) as well as lower serum "Total protein" levels ($p = 0.001$) and lower serum "Globulin" levels ($p < 0.001$) (Table 25). Among the analysed parameters MARF cases with the need for RRT showed a significant lower "Urine output" ($p = 0.001$), higher "WBC" counts ($p = 0.01$), higher "AST" levels ($p = 0.002$), higher "Urine specific gravity" ($p = 0.035$) and higher "Urine RBC" counts ($p = 0.004$) (Table 27). Laboratory parameters which were found to be significantly related to the outcome of RRT were high "WBC" counts ($p = 0.005$), prolonged "PTT" (partial thromboplastin time) ($p = 0.034$), low "HCO_3^-" levels ($p = 0.008$), low serum "Sodium" ($p = 0.012$), high serum "Potassium" ($p = 0.037$), low serum "Chloride" ($p = 0.037$), high "AST" levels ($p = 0.029$), low serum "Total protein" levels ($p = 0.046$) and low serum "Globulin" levels (Table 29).

Table 25: Baseline laboratory parameters in relationship to survival and death.

Baseline laboratory parameters	Units	Outcome: Survival n	Median	Range	Mean	S.D.	Death n	Median	Range	Mean	S.D.	p-value
Temperature	°C	56	38.2	36.0-40.2			20	38.6	36.0-40.6			0.184
Pulse rate	/min	56	108	62-160			20	121	89-158			0.072
Blood pressure sys.	mmHg	56	100	80-160			32	100	80-160			0.596
Blood pressure dia.	mmHg	56	60	41-100			32	60	27-116			0.480
Output urine	ml/24h	38	200	2-2900			16	95	0-2000			0.113
Hb	g%	55			10.3	2.9	19			10.0	3.6	0.698
Hct	%	56			29.8	9.4	19			28.8	11.1	0.708
RBC	x 10^{2}/l	55	3.6	1-7			19	3.2	1-5			0.536
WBC	x 10^{6}/l	55	7.3	3-35			19	13.9	3-61			<0.001
Neutrophiles	%	54	72.1	9-88			19	76.0	51-87			0.197
Lymphocytes	%	54	19.1	8-85			19	16.0	7-38			0.375
Platelet-count	x 10^{9}/l	54	27.0	3-302			19	30.0	5-164			0.841
PT	sec.	20	15.6	11-59			11	17.7	10-60			0.403
PTT	sec.	19	35.8	23-120			11	42.3	21-133			0.103
INR	-	20	1.37	1-6			11	1.75	1-7			0.133
HCO_3^-	mmol/l	52	15.4	5-23			19	10.9	4-17			0.001
Sodium	mmol/l	52	133	117-148			19	131	112-145			0.533
Potassium	mmol/l	52	3.95	1.2-6.0			19	4.38	2.9-8.5			0.106
Chloride	mmol/l	52	99	84-114			19	98	80-115			0.370
Creatinine	mg%	56	5.4	1.7-18.0			19	5.7	1.4-9.9			0.439
BUN	mg%	56	82	17-213			19	94	24-194			0.563
Bilirubin total	mg%	45	11.1	0.4-30.1			14	4.95	1.9-32.5			0.929
direct Bilirubin	mg%	45	3.4	0.1-93.0			14	1.7	0.6-12.8			0.852
AST	U/l	47	106	9-969			14	305	40-1897			0.001
ALT	U/l	47	67	14-3731			14	130	39-571			0.015
Alk. Phosphatase	U/l	46	108	42-649			14	121	93-356			0.181
Total Protein	g%	46	5.7	3.4-7.8			14	4.9	3.9-5.9			0.001
Albumin	g%	46	2.7	1.5-3.7			14	2.5	1.7-3.3			0.250
Globuline	g%	46	2.8	1.9-5.0			15	2.3	1.9-3.2			<0.001
Urine pH	-	33	6	5-6			15	6	5-7			0.206
Urine specifi. grav.	g/l	33	1020	1005-1030			15	1025	1005-1050			0.099
Urine RBC	/HPF	34	4	0-100			15	10	1-100			0.310
Urine WBC	/HPF	34	3	1-10			15	4	1-15			0.424

Table 26: Baseline urine albumin level in relationship to survival and death.

Urine albumin	Total number of cases n	%	Outcome: Survival n	%	Death n	%
	49		34		15	
0	9	18.4	5	55.6	4	44.4
1+	18	36.7	14	77.8	4	22.2
2+	15	30.6	11	73.3	4	26.7
3+	6	12.3	3	50.0	3	50.0
4+	1	2.0	1	100	0	0

Urine albumin	Total number of cases n	%	Outcome: Survival n	%	Death n	%	p-value
0 – 1+	27	55.1	19	70.4	8	29.6	0.869
2+ – 4+	22	44.9	15	68.2	7	31.8	

Table 27: Baseline laboratory parameters in relationship to the use of RRT.

Baseline laboratory parameters	Units	Outcome: No RRT n	Median	Range	Mean	S.D.	Outcome: RRT n	Median	Range	Mean	S.D.	p-value
Temperature	°C	44	38.3	36.0-40.5			32	38.2	36.0-40,6			0.962
Pulse rate	/min	44	110	66-160			32	110	62-158			0.950
Blood pressure sys.	mmHg	43	100	80-160			32	100	80-160			0.401
Blood pressure dia.	mmHg	43	60	41-100			32	60	27-116			0.831
Output urine	ml/24h	28	350	20-2000			26	100	0-2900			0.001
Hb	g%	42			10.2	3.1	32			10.2	3.1	0.998
Hct	%	43			29.4	10.0	32			29.6	9.6	0.940
RBC	x 10^2/l	42	3.55	2-7			32	3.43	1-6			0.608
WBC	x 10^6/l	42	6.8	3-35			32	9.7	3-61			0.010
Neutrophiles	%	42	71.5	9-88			31	73.7	58-88			0.269
Lymphocytes	%	42	21.0	9-85			31	16.0	7-35			0.059
Platelet-count	x 10^9/l	42	28.5	3-302			31	29.0	3-164			0.867
PT	sec.	16	15.8	11-60			15	15.5	10-35			0.441
PTT	sec.	15	39.4	21-133			15	35.3	28-60			0.351
INR	-	16	1.51	1-7			15	1.38	1-4			0.649
HCO_3^-	mmol/l	40	15.3	6-21			31	14.3	4-23			0.330
Sodium	mmol/l	40	131	117-145			31	133	112-148			0.462
Potassium	mmol/l	40	3.9	2.6-6.0			31	4.0	1.2-8.5			0.291
Chloride	mmol/l	40	99	84-114			31	99	80-114			0.776
Creatinine	mg%	43	4.9	1.7-18.0			32	6.0	1.4-14.6			0.974
BUN	mg%	43	86	17-213			32	82	24-195			0.849
Bilirubin total	mg%	31	7.4	0.4-31.2			28	12.5	1.1-32.5			0.093
direct Bilirubin	mg%	31	2.9	0.1-12.8			28	4.0	0.4-11.3			0.184
AST	U/l	33	78	9-1638			28	238	62-1897			0.002
ALT	U/l	33	63	14-3731			28	89	20-515			0.116
Alk. Phosphatase	U/l	32	111	42-649			28	109	54-356			0.965
Total Protein	g%	32	5.7	4.0-7.8			28	5.4	3.4-6.9			0.320
Albumin	g%	32	2.6	1.7-3.5			29	2.7	1.5-3.7			0.856
Globuline	g%	32	2.8	2.1-5.0			28	2.7	1.9-3.7			0.176
Urine pH	-	26	6	5-7			22	6	5-6			0.585
Urine specif. grav.	g/l	26	1020	1005-1030			22	1023	1005-1050			0.035
Urine RBC	/HPF	26	1.5	0-40			23	15	1-100			0.004
Urine WBC	/HPF	26	2.5	1-10			23	3	1-15			0.315

Table 28: Baseline urine albumin level in relationship to the use of RRT.

Urine albumin	Total number of cases n	%	Outcome: No RRT n	%	Outcome: RRT n	%
	49		27		22	
0	9	18.4	5	55.6	4	44.4
1+	18	36.7	13	72.2	5	27.8
2+	15	30.6	6	40.0	9	60.0
3+	6	12.3	2	33.3	4	66.7
4+	1	2.0	1	100	0	0

Urine albumin	Total number of cases n	%	Outcome: No RRT n	%	Outcome: RRT n	%	p-value
0 – 1+	27	55.1	18	66.7	9	33.3	0.071
2+ – 4+	22	44.9	9	40.9	13	59.1	

Table 29: Baseline laboratory parameters at the initiation of RRT in relationship to survival and death in RRT.

Baseline laboratory at initiation of RRT	Units	Outcome										p-value
		RRT - Survival					RRT - Death					
		n	Median	Range	Mean	S.D.	n	Median	Range	Mean	S.D.	
Temperature	°C	20	38.0	36.0-39.6			12	39.0	36.5-40.6			0.072
Pulse rate	/min	20	108	62-136			12	119	80-158			0.338
Blood pressure sys.	mmHg	20	110	81-140			12	93	80-160			0.204
Blood pressure dia.	mmHg	20	68	44-92			12	50	27-116			0.073
Output urine	ml/24h	20	105	2-2900			11	60	0-850			0.145
Hb	g%	20			9.9	3.1				10.7	3.4	0.474
Hct	%	20			28.8	9.2				31.0	10.4	0.547
RBC	x 10^2/l	20	3.3	1-6			12	3.8	1-5			0.414
WBC	x 10^6/l	20	8.8	3-18			12	13.5	8-61			0.005
Neutrophiles	%	19	73.7	58-88			12	75.2	59-87			0.503
Lymphocytes	%	19	16.0	8-35			12	15.7	7-26			0.626
Platelet-count	x 10^9/l	19	26.0	3-55			12	29.5	11-164			0.598
PT	sec.	9	14.6	13-20			6	17.9	10-35			0.409
PTT	sec.	9	31.4	28-55			6	45.0	34-60			0.034
INR	-	9	1.35	1-2			6	1.92	1-4			0.087
HCO_3^-	mmol/l	19	15.5	5-23			12	7.3	4-17			0.008
Sodium	mmol/l	19	135	122-148			12	131	112-141			0.012
Potassium	mmol/l	19	4.0	1.2-5.7			12	5.0	3.4-8.5			0.037
Chloride	mmol/l	19	100	93-114			12	96	80-105			0.037
Creatinine	mg%	20	6.1	2.2-14.6			12	6.0	1.4-9.9			0.726
BUN	Mg%	20	90	36-195			12	74	24-194			0.984
Bilirubin total	mg%	19	13.3	1.1-30.1			9	5.4	2.4-32.5			0.476
direct Bilirubin	mg%	19	4.4	0.4-10.4			9	1.8	0.8-11.3			0.507
AST	U/l	19	184	62-969			9	354	123-1897			0.029
ALT	U/l	19	71	20-253			9	130	39-515			0.069
Alk. Phosphatase	U/l	19	108	54-229			9	132	93-356			0.153
Total Protein	g%	19	5.6	3,4-6.9			9	5.0	3.9-5.9			0.046
Albumin	g%	19	2.5	1.5-3.7			10	2.8	1.9-3.3			0.712
Globuline	g%	19	2.7	1.9-3.7			9	2.2	1.9-3.2			0.004
Urine pH	-	13	6	5-6			9	6	5-6			0.090
Urine specif. grav.	g/l	13	1020	1005-1030			9	1025	1015-1050			0.082
Urine RBC	/HPF	14	15	1-100			9	15	1-100			0.924
Urine WBC	/HPF	14	3	1-10			9	4	2-15			0.118

Table 30: Baseline urine albumin level in relationship to the outcome of RRT.

Urine albumin	Total number of cases		Outcome			
			RRT-Survival		RRT-Death	
	n	%	n	%	n	%
	22					
0	4	18.2	1	25.0	3	75.0
1+	5	22.7	3	60.0	2	40.0
2+	9	40.9	7	77.8	2	22.2
3+	4	18.2	2	50.0	2	50.0
4+	0	0	0	0	0	0

Urine albumin	Total number of cases		Outcome				p-value
			RRT-Survival		RRT-Death		
	n	%	n	%	n	%	
0 – 1+	9	40.9	4	44.4	5	55.6	0.384 *
2+ – 4+	13	59.1	9	69.2	4	30.8	

7. Logistic regression analysis of the identified statistically significant associated putative risk factors in relationship to the different outcomes

Firstly the clinical, therapeutical and paraclinical parameters, which showed a statistically significant association with the three outcomes "Survival vs. Death", "RRT vs. no RRT" and "RRT-Survival vs. RRT-Death" were identified by analysing the "Presenting symptoms at the time of admission", the "Renal failure classification / Therapeutical intervention", the "WHO-criteria for severe malaria" and the laboratory parameters (Table 14 - 18, 22 - 25, 27, 29). After identifying the significant parameters and pooling them as displayed below (Table 31), logistic regression analysis was used to adjust for confounding factors and determine the ranking and individual importance of the identified putative risk factors for outcome-prediction among each of the three outcome-groups. In the logistic regression model for the outcome-group "Survival vs. Death", only the factors "Mechanical ventilation" ($p = 0.028$) and the serum "Globulin" level ($p = 0.017$) retained a statistically significant relationship. In the logistic regression model for the outcome-group "No RRT vs. RRT" only the use of "Inotropic drugs" ($p = 0.035$) remained significant (Table 32). In the logistic regression analysis of the outcome-group "RRT-Survival vs. RRT-Death" none of the analysed parameters retained any statistical significance.

Table 31: The identified statistically significant putative risk factors according to the different outcome-groups.

Putative risk factors ($p < 0.05$)	**Outcome**		
	Survival / Death	**RRT / no RRT**	**RRT-Survival / RRT-Death**
Impairment of consciousness	+	+	+
GCS < 10	+	+	+
Mechanical ventilation	+	+	+
Circulatory collapse / Inotropic drugs	+	+	+
FFP transfusion	+	+	+
WBC	+	+	+
AST	+	+	+
Metabolic acidosis / HCO_3^-	+	–	+
Total serum protein & Globulin	+	–	+
Pulmonary oedema / ARDS	–	+	+
Hepatomegaly	+	–	–
ALT	+	–	–
Coma	+	–	–
Transfusion of blood products	–	+	–
RBC transfusion	–	+	–
Anuria / Oliguria	–	+	–
Hypercatabolic state	–	+	–
Urine RBC	–	+	–
Urine specific gravity	–	+	–
Urine output	–	+	–
PTT	–	–	+
Potassium	–	–	+
Chloride	–	–	+
Sodium	–	–	+

+ = statistical significance ($p < 0.05$) ; – = no statistical significance ($p > 0.05$)

Table 32: Result of the logistic regression analysis of the identified statistically significant putative risk factors.

Outcome Survival / Death				
Variables	**Total number of cases**	**Adjusted odds ratio**	**95% CI**	**p-value**
	38			
Mechanical ventilation		154.960	1.700 – 14122.957	0.028
Serum Globulin		0.017	0.001 – 0.479	0.017

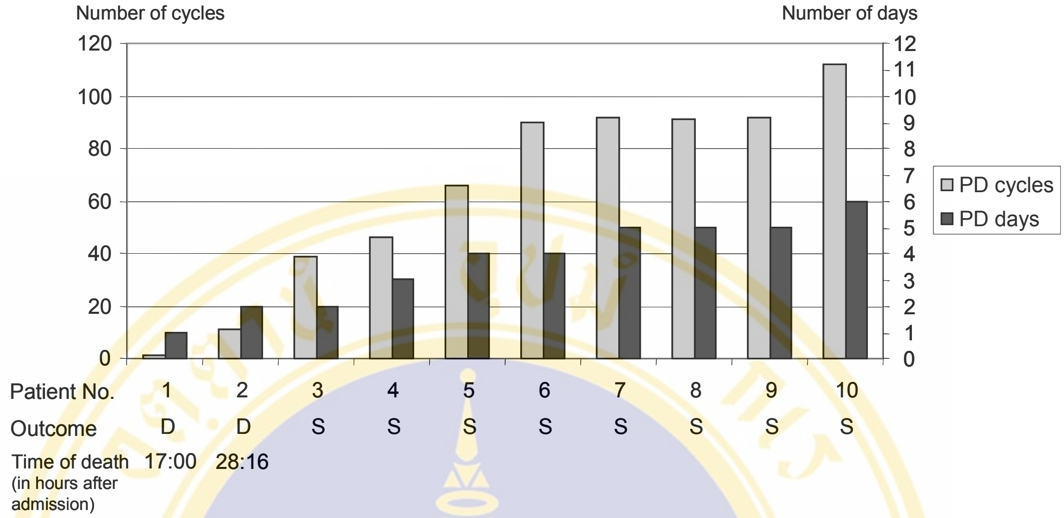
Outcome RRT / no RRT				
Variables	**Total number of cases**	**Adjusted odds ratio**	**95% CI**	**p-value**
	19			
Inotropic drugs		27.000	1.260 – 578.354	0.035

8. The observed baseline-characteristics, dialysis-frequencies, dialysis-durations and outcome of the different RRT modalities among the studied MARF patients.

Due to the incomparable baseline conditions, a statistical analysis comparing the outcome of the different dialysis modality groups (PD, HD, and the combination of PD and HD) among each other has been omitted. A descriptive overview over the baseline laboratory findings at the initiation of dialysis and a quantification of RRT-cycles and -duration of the 32 dialysed patients is given in Figure 12, 13 and 14.

32 (42.1%) of the 76 MARF patients received RRT: 16 patients were treated with HD, 10 patients with PD and 6 patients received consecutively PD and HD (Table 18). While 6 of the 16 patients receiving HD died (37.5%), 2 of the 10 patients receiving PD died (20%) and 4 of the 6 patients treated with PD and HD died (66.7%)(Table 18). The MARF patients successfully treated with HD received a median of 2.5 cycles (Range: 1 - 9) applied over a median time of 8 days (Range: 1 - 13) (Figure 13). The MARF patients successfully treated with PD received a median of 90.5 cycles (Range: 39 - 112) applied over a median time of 4.5 days (Range: 2 - 6) (Figure 12). The number of dialysis cycles and duration of RRT in the patients treated with PD and HD consecutively is depicted in Figure 14.

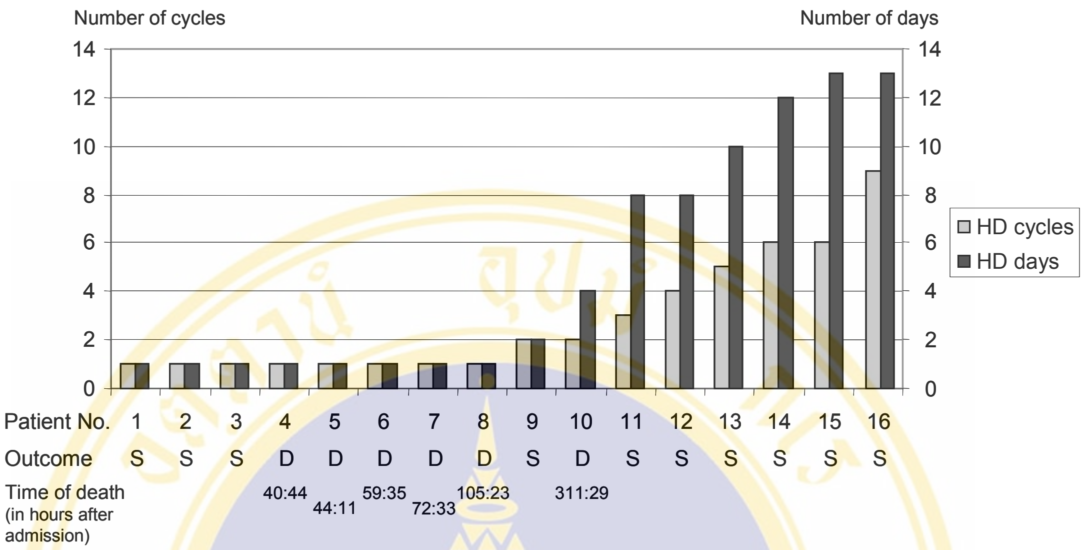
Peritoneal dialysis



Pat. ID	6	42	84	5	69	24	78	77	22	80
Urine-output	10	10	-	2900	220	105	-	200	200	150
HCO_3^-	5.9	15.4	16.2	5.0	17.7	15.2	11.1	18.1	12.0	11.3
Potassium	5.56	8.48	3.99	3.1	4.39	3.13	3.78	4.26	3.72	4.29
Creatinine	3.4	5.7	3.1	3.0	6.5	5.6	14.6	2.2	4.7	7.1
BUN	74	58	82	81	107	54	166	45	56	158
AST	256	1897	288	67	84	403	75	191	398	184
WBC	13	5	6	8	18	10	9	5	9	15
Total protein	5.6	4.1	5.7	3.4	5.7	5.4	5.1	6.9	5.1	5.6
Globuline	2.5	2.2	3.2	1.9	3.7	2.7	3.0	3.6	3.0	3.3
Urine specif.grav.	1030	-	1025	1025	-	-	1015	1030	1015	-
Urine RBC	25	-	15	15	-	-	4	1	4	-

Figure 12: Overview of the 10 patients treated with peritoneal dialysis.

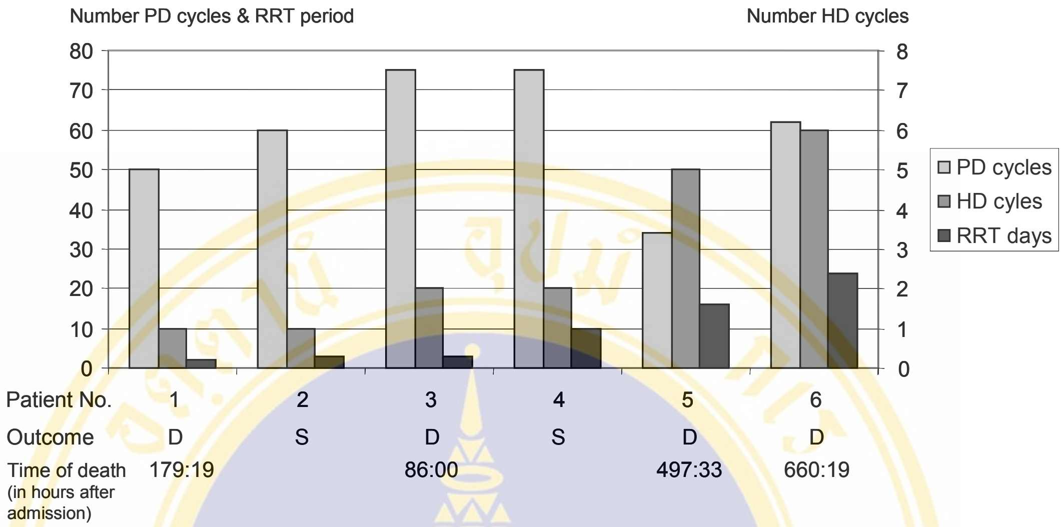
Haemodialysis



Pat. ID	27	34	46	30	52	32	38	73	75	76	54	49	62	53	3	83
Urine-output	200	-	50	700	120	150	850	60	20	25	-	100	30	100	100	150
HCO_3^-	19.2	-	12.0	16.2	18.8	16.1	10.3	14.4	17.6	5.3	15.9	15.5	23.4	13.5	17.7	18.3
Potassium	4.23	-	3.74	3.42	4.71	5.34	3.99	4.65	4.49	3.39	4.32	3.74	3.88	4.04	3.47	1.17
Creatinine	2.9	4.3	11.7	1.4	1.7	7.2	6.2	9.4	8.7	7.2	6.9	9.7	3.9	2.4	2.3	2.3
BUN	36	48	195	24	61	194	74	101	173	145	97	119	71	43	50	39
AST	495	345	300	354	64	123	214	220	-	685	122	62	82	106	969	409
WBC	9	8	15	9	6	9	11	19	11	13	14	6	3	5	8	7
Total protein	5	6.7	5.9	5.3	5.1	5.4	3.9	5.0	-	4.2	5.5	5.9	5.0	5.2	6.9	5.8
Globuline	2.6	3.0	3.6	2.0	2.1	2.6	1.9	2.2	-	2.0	2.7	3.4	2.7	2.5	3.7	2.5
Urine specif. grav.	1025	-	1022	1015	1020	1025	1020	1025	1010	1030	-	-	1025	1005	-	1010
Urine RBC	1	-	100	100	40	2	15	100	10	1	-	-	10	15	15	100

Figure 13: Overview of the 16 patients treated with haemodialysis.

Peritoneal + Haemodialysis



Pat. ID	40	44	39	81	58	82
Urine-output	0	600	0	0	90	-
HCO_3^-	16.9	14.1	4.4	14.3	8.0	5.3
Potassium	3.54	4.03	6.77	5.68	4.38	7.3
Creatinine	2.7	8.4	6.9	7.3	8.7	3.0
BUN	58	134	134	125	144	55
AST	-	116	-	324	712	-
WBC	8		14	10	21	61
Total protein	-	6.0	-	4.9	5.9	-
Globuline	-	2.7	-	2.5	3.2	-
Urine specif. grav.	1020	1020	-	1020	1025	-
Urine RBC	2	100	-	40	4	-

Figure 14: Overview of the 6 patients treated with peritoneal- and haemodialysis.

Fatal cases who were not treated with RRT

Pat. No. 1 28 years old, male, Burmese

Referred from community hospital with a history of upper-gastro-intestinal-bleeding, referred on mechanical ventilation and catecholamines.

Jaundice, impaired consciousness, respiratory failure, circulatory collapse (need for catecholamines), history of spontaneous upper gastrointestinal bleeding, laboratory was suspended after patient expired (no data available).

Death 1h 30min after admission.

Suspected causes of death: cerebral malaria, respiratory failure, circulatory failure, MARF.

Pat. No. 2 4 years old, male, Burmese

Referred from Malaria-Clinic.

Impaired consciousness, circulatory collapse (need for catecholamines), metabolic acidosis (pH 6.9, HCO_3 5.6), hypoglycemia, respiratory failure (mechanical ventilation), WBC 26.7, Plt. 17, PTT 42.3, INR 4,

Exchange transfusion was performed.

Death 6h:56min after admission.

Suspected causes of death: cerebral malaria, respiratory failure, circulatory failure, metabolic acidosis, liver failure, sepsis, MARF

Pat. No. 3 32 years old, male, Burmese

Referred form Mae-Tao-Clinic.

Jaundice, anemia, hepatosplenomegaly, Coma (GCS 8), metabolic acidosis (HCO_3 12.4), Plt. 5, Crea 7.9, BUN 120

RRT was planed but patient expired before.

Death 17h:06min after admission.

Suspected cause of death: cerebral malaria, metabolic acidosis, MARF.

Pat. No. 5 69 years old, male, Thai

Direct admission.

Impaired consciousness on admission (GCS 12), circulatory collapse (need for catecholamines), respiratory failure (mechanical ventilation), metabolic acidosis (HCO_3 13.4), Plt. 45, Crea 3.9, BUN 32.

RRT planed but insertion of dialysis catheter failed.

Death 27h:44min after admission.

Suspected cause of death: cerebral malaria, respiratory failure, circulatory failure, metabolic acidosis, MARF.

Pat. No. 7 35 years old, female, Burmese

Referred from community hospital.

Jaundice, anemia, hepatomegaly, metabolic acidosis (pH 7.2, HCO_3 16.4), respiratory failure (mechanical ventilation), documented cardio-pulmonary-resuscitation, Crea 7.8, BUN 98, WBC 16.6.

RRT was planed but patient died before.

Death 29h:20min after admission.

Suspected cause of death: respiratory failure, circulatory failure, metabolic acidosis, sepsis, MARF.

Pat. No. 9 32 years old, female, Burmese

Referred from Mae-Tao-Clinic.

Jaundice, anemia, hepatomegaly, coma (GCS 8), circulatory collapse (need for catecholamines), respiratory failure (mechanical ventilation), metabolic acidosis (HCO_3 12.8), WBC 18, Plt. 26, Crea 11.2, BUN 177.

RRT was planed but insertion of dialysis catheter failed.

Death 43h:34min after admission.

Suspected cause of death: cerebral malaria, respiratory failure, circulatory failure, metabolic acidosis, sepsis, MARF.

Pat. No.11 15 years old, male, Burmese

Referred form community hospital with a history of upper-gastro-intestinal-bleeding, referred on mechanical ventilation (pneumothorax [on chest tube]) .

Jaundice, coma (GCS 8), severe anemia (Hct 14.7), circulatory collapse (need for catecholamines), respiratory failure (mechanical ventilation), metabolic acidosis (HCO_3 16.6), multiple convulsions, liver failure (PTT 66.2, INR 7, AST 1481), WBC 19.3, Plt 19, Crea 3.1, BUN 119.

Urine culture: *Klebsiella spp., E.coli*.

Death 45h:16min after admission.

Suspected cause of death: cerebral malaria, respiratory failure, circulatory failure, liver failure, metabolic acidosis, sepsis, MARF.

Pat. No.12 55a, female, Burmese

Direct admission.

GCS 9, circulatory collapse (need for catecholamines), respiratory failure (mechanical ventilation), metabolic acidosis (pH 6.9, HCO_3 5.5), liver failure (INR 1.48, AST 1638), WBC 49.6, Plt. 32, Crea 4.9, BUN 149.

Death 53h:54min after admission.

Suspected cause of death: cerebral malaria, respiratory failure, circulatory failure, liver failure, sepsis, MARF.

As clearly obvious from the descriptions above, none of the fatal cases who were not dialysed died without multi-organ-failure. Multi-organ-failure was present in all cases.

9. The frequency distribution of complications present at time of death

The frequency-distribution of the different complications present at the time of death among the 20 fatal MARF cases has been reconstructed from the medical records (including available laboratory figures and the physicians' notes as available) and is shown in Figure 15.

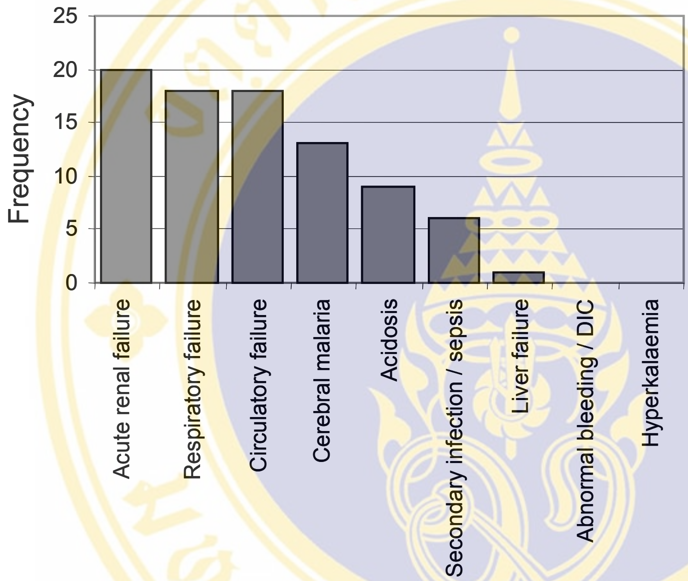


Figure 15: The frequency-distribution of complications present at time of death

CHAPTER VI
DISCUSSION

1. Study limitations and restrains

Before discussing the results of the collected data, the restrictions and limitations of this retrospective study should be briefly outlined and highlighted:

1. Despite the carried out sample-size calculation and the prior review of the probably available data it was not possible to reach the estimated sample-size. The underlying problems were mostly files being classified as MARF despite not fulfilling the criteria for MARF and the much higher than expected number of cases presenting with concomitant infections (Figure 2).
2. The available data were rather limited and in many cases it was neither possible to reconstruct the patient's course of illness nor the rational of some treatment measures. Especially data about referred cases to Mae Sot General Hospital did almost never exist as referral letters are exceptional and even if existing not conclusive in most cases. This is particularly important as a high percentage of cases included in this study were referred cases (see below).
3. The lack of treatment guidelines concerning the approach to patients with MARF creates an unequal baseline making the comparison of outcome differences rather unreliable.
4. The patients treated with RRT received different modalities of dialysis (peritoneal dialysis, haemodialysis, or a combination of peritoneal and haemodialysis). The choice of treatment modality is in this connexion rather determined by the availability of a physician trained in performing haemodialysis than by the degree and severity of the patient's renal dysfunction. Therefore a reasonable comparison of the different RRT modalities is impossible and has been omitted.

2. Seasonal pattern of malarial acute renal failure cases at Mae Sot General Hospital

Mae Sot district is a hypo-endemic, low / unstable malaria-transmission area with approximately one infection per person per year (Luxemburger et al., 1997). Paul et al. reported a seasonal malaria-transmission pattern around Mae Sot with two peaks between May and July and November and January (Paul et al., 1998). This seasonal transmission-pattern is also reflected and visible in the seasonal frequency of the 76 MARF cases investigated in this study (Figure 3).

3. Demographic data

The distribution of severe malaria manifestations including MARF is known to be largely depended on epidemiological factors (Local endemicity, transmission patterns, and degree of premunition) and the age of the exposed population (White, 2003a). In South-East Asia severe malaria is known to affect all age groups (WHO, 2006b). This fact is reflected by the wide age range (4 to 74 years) of the 76 cases covered in this study. The low number of children observed among the studied MARF cases can be explained by the reported lower incidence of MARF in children compared to adults in South-East Asia (WHO, 2006b). The most affected age-group in this study is the working age-group between ~ 25 and ~ 40 years old (Median 33.5 (4 - 74) years [Figure 4]). Very similar age-medians of MARF patients were reported from a series of 112 MARF patients studied at the Bangkok Hospital for Tropical Diseases with an median age of 30.4 (Range: 11 - 71) years and from a referral center for MARF cases in South Vietnam, were the efficacy of peritoneal dialysis was compared to haemofiltration: The median age in the two studied groups was 36.0 (Range: 29.6 - 38.4) and 35.0 (Range: 29.5 - 38.2) years respectively (Wilairatana et al., 1999; Phu et al., 2002). From an Indian MARF study a median age of 31.5 (Range: 15 - 85) years has been reported (Prakash et al., 1996). In a hypoendemic, low / instable transmission area for malaria the high incidence of MARF in this age-group reflects the absence of premunition combined with the increased occupational exposure of this age-group to the mosquito vector (White, 2003a). The most exposed population is supposed to be the ones working in the agricultural and forest operation sectors. Around Mae Sot most employments can be attributed to this sector. The available occupational data of the studied MARF patients show a proportion of 16% specifying their occupation as "farmers", whereas 78.7% specified their occupation as "labour" (Table 5). The amazingly low proportion of "farmers" becomes more transparent when a subgroup-analysis is performed: Whereas none of the Burmese patients is found among the "farmers", 42.9% of the Thai patients specified their occupation as "farmers". This figures could be explained by the fact, that the Burmese population living in Thailand is - in contrast to the Thai residents - unskilled, not owning land and mostly working as employed "labourers" in the agricultural and forest operation sector. It can be speculated whether the 50% of Thai cases, who specified their occupation as "labourers" are working in a similar relationship as the Burmese workers. Unfortunately there is not more detailed information about the patients' occupational background. The exclusive Burmese patients in the age-group 13 to 25 years and the overall higher proportion of male patients among the studied cases (Figure 5) could be explained accordingly: exposure. No contribution can be made to the question whether there is a gender related difference in the susceptibility to renal dysfunction and renal failure in severe malaria patients (Wilairatana et al., 1999) by this study, as only MARF were studied. Even if gender related susceptibility is existing, neither the outcome of MARF (Table 11) nor the need for RRT (data not displayed) shows a statistically significant difference between the male and female patients.

According to the hospital records 54% of the treated malaria patients at Mae Sot General Hospital in the years 2003 to 2006 were ethnic Thai, while Burmese patients were accounting for 43% and local hill-tribes / ethnic minorities for the remaining 3% of all cases. The discrepancy between this overall higher proportion of Thai patients among the treated malaria cases but lower proportion of Thai patients among the MARF cases in this study (36.8% Thai, 63.2% Burmese [Table 5]) might be explained by socioeconomic factors influencing the access to, and the presenting time at health facilities: hypothetically the socioeconomic weaker Burmese patients present later at health facilities and are - as severe manifestations of malaria are usually the result of delayed treatment of uncomplicated malaria (WHO, 2006b) - more prone to develop complications like MARF.

4. Presenting symptoms prior to admission

The data about the onset and nature of symptoms prior to admission was collected according to the notes in the patients' medical records. As the notes are mostly "positive" reports (In the absence of a form for recording the different symptoms as "present" or "absent" it is more likely that the physician in charge is writing down symptoms the patient is complaining about rather than symptoms the patient is not complaining about), the data has to be seen as a rather rough descriptive picture (Figure 6). The frequency distribution of the different symptoms prior to admission in relation to the outcomes "Survival vs. Death" and "No RRT vs. RRT" is listed in table 6 and 7. Due to the mentioned weakness of the data further statistical analysis has been omitted. In order to identify putative risk factors for outcome or the need for RRT among the different clinical symptoms more complete data would have to be available. For example a history of decreased urine-volume could be assumed to be a risk factor associated with the development of MARF and the need for RRT: unfortunately information about the amount of voided urine prior to admission was present in less than 28% (Table 6 and 7).

MARF is considered a complication of malaria manifesting if treatment is delayed (WHO, 2006b). Therefore it was tried to assess the time span from the onset of the first symptoms to the start of medical treatment (Figure 7) and to look for putative relations between the time span of untreated malaria and the outcomes "Survival vs. Death" and "No RRT vs. RRT" among the studied MARF cases. The hypothetical assumption was that longer delay of proper treatment is resulting in a higher demand for RRT and a higher case fatality rate.

The major problem with the collected data about "Symptoms of illness prior to admission" is, that 50% of the MARF cases in this study are referred cases: Even so information about the symptoms prior to admission was obtainable in most cases, data about the length of hospitalization prior to referral (as well as proper diagnostic and treatment information) was even in the rare case of an existing referral-note not available in the majority of cases. The presented data therefore probably show a too short time span (Median: 4 days, Range: 1 - 10 days) between the onset of symptoms and the presentation of MARF when compared to the available published data mostly describing a median of 5.4 to 7 days before the presentation of MARF (Wilairatana et al., 1999; Nacher et al., 2001b; Phu et al., 2002). Obtaining proper information about the onset of symptoms prior to admission and the time of hospitalization prior to referral would be necessary for further evaluation of the exact time-course of MARF and the relation between time, the need for RRT and outcome.

5. Case fatality rate / Outcome of MARF cases at Mae Sot General Hospital

The 76 MARF cases covered by this study showed an overall case fatality rate of 26.3% (Table 13). In the light of a study carried out at a referral center for severe malaria cases in Vietnam where the introduction of peritoneal dialysis was able to reduce the case fatality rate of MARF from 75% to 26% (Trang et al., 1992) a case fatality rate of 26.3% might - on first glance - look disappointing for a setting, where even superior RRT facilities in the form of haemodialysis are available. It becomes even more disappointing if we look on the lowest ever published case fatality rate in MARF reported from a study conducted at the Bangkok Hospital for Tropical Diseases: 10.7% (Wilairatana et al., 1999). When comparing this figure some considerations have to be made: Early haemodialysis applied by highly trained staff, available around the clock is usually confined to specialized centres such as the Bangkok Hospital for Tropical Diseases, whereas in settings like Mae Sot General Hospital - even though haemodialysis facilities are available - RRT is usually limited to working days and normal daytime working hours, as physicians experienced in RRT are not readily available at nighttimes, weekends or public holidays. The same considerations have to be taken into account for other intensive care measures, which might be of pivotal importance in the not infrequent observed MARF patients presenting with multi-organ-failure (Krishnan and Karnad, 2003). Therefore - even though efforts aiming for decreasing the case fatality rate in MARF should always be made - an overall MARF case fatality rate of 26.3% is a rather good outcome for a district hospital setting compared with the above mentioned case fatality rates ranging from 10.7% (Bangkok, Hospital for Tropical Diseases) to 26% (Vietnam, Ho Chi Min City Center for Tropical Diseases) in highly specialized centres.

Compared to our 26.3% an almost identical MARF case fatality rate has been reported from a referral center for severe malaria in Pakistan: 26% (Naqvi et al., 2003).

On the other side of the scale high case fatality rates of 57.9% found among MARF patients at a General Hospital setting in Malaysia (Koh et al., 2006) and 52.8% reported from an Indian ICU setting (Krishnan and Karnad, 2003) have been published. These high case fatality rates are all the more astonishing when considering the good ICU and RRT facilities present in these settings: In both settings even continuous forms of RRT were available and used in some patients.

Whether differences in malaria endemicity, population susceptibility, parasite virulence, local referral policies or experience in treating MARF patients can explain the wide range of the observed case fatality rates is difficult to answer and could be discussed.

Considering, that Mae Sot General Hospital is a referral center for MARF patients and that the outcome of MARF is supposed to be largely depending on early referral and treatment, a subgroup analysis of the 76 studied cases was performed to determine outcome-differences between "Direct admitted" and "Referred" MARF cases. Before looking on the results of the statistical analysis, the background of the referral institutions needs to be described. The referral institutions include four local community hospitals, a local outpatient Malaria Clinic, MSF (Médecins-Sans-frontières) and Mae-Tao-Clinic:

1. Community hospitals: The community hospitals have basic medical facilities, a laboratory and a trained physician. When it comes to intensive care, mechanical ventilation in case of respiratory failure is possible, but cases of ARF with the need for RRT are referred to Mae Sot General Hospital. Despite the fact, that peritoneal dialysis is an available treatment option on community hospital level, none of the cases investigated in this study had peritoneal dialysis performed prior to referral.
2. Malaria Clinic: Facility for testing and treating patients on an outpatient base. In case of complicated malaria, immediate referral to Mae Sot General Hospital is the practice.

3. MSF (Médecins Sans frontières): A non-government-organisation (NGO) providing basic inpatient and outpatient medical facilities to Burmese refugees on the Thai side of the Thai-Burmese border. The available facilities are limited to basic medical care and basic laboratory tests. Referral of patients is depending on the available budget situation and judgment of the medical staff.
4. Mae-Tao-Clinic: A non-profit Burmese refugee clinic financed by donations, which provides inpatient and outpatient medical facilities and treatment to Burmese refugees on the outskirts of Mae Sot. The available facilities are limited to basic laboratory (Blood glucose, Malaria microscopy and Hb) with referrals being exceptional due to the lack of financial resources.

For further statistical analysis the MARF cases direct admitted at Mae Sot General Hospital were pooled with the MARF cases referred from the Malaria Clinic (n = 3). The rational background of pooling these cases is the similar span of time between diagnosis and treatment in this group of patients: After a positive malaria test and the presence of complications the patients are immediately referred to Mae Sot General Hospital, where (as the diagnosis is already established) treatment can be started without delay.

Among the patients referred from the institutions with an inpatient setting the MARF cases referred from Mae-Tao-Clinic were pooled with the referral from MSF (n = 1). The rational background for pooling these cases is the following:

1. Similar (if not the same) diagnostic and treatment facilities
2. Referral of patients is largely depending on the prevailing budget-situation and rather exceptional. Because of this referrals are delayed and late compared with the referrals from the community hospitals.

The subgroup analysis shows that the MARF cases directly admitted at Mae Sot General Hospital have a statistically significant lower case fatality rate than the referred cases (15.8% vs. 36.8% [Table 13]). The case fatality rate of patients pre-treated at community hospital level and later referred to Mae Sot General Hospital for RRT is 27.3%. Even though statistical significance (compared to direct admission at

Mae Sot General Hospital: 15.8% vs. 27.3%) can not be proven (Table 13), the observed higher case fatality rate could reflect the degree of delayed treatment, which is suspected to be of crucial importance. A strong statistical significance can be demonstrated between the cases directly admitted at Mae Sot General Hospital and the cases referred from Mae-Tao-Clinic and MSF (15.8% vs. 50%) (Table 13).

Considering that facilities and experienced staff for malaria microscopy are equally available and malaria treatment is based on Artemisinin based combination therapy (ACT) regardless of the different settings, the difference in outcome among the MARF cases can mostly be attributed to the availability of laboratory facilities (for detecting renal impairment and diagnosing acute renal failure), proper supportive care by trained staff and the availability / delay of intensive-care treatment such as RRT, mechanical ventilation or shock management. The time factor of delayed treatment in MARF has been a well reported risk factor from different studies (Wilairatana et al., 1999; Barsoum, 2000; WHO, 2006b; Kaur et al., 2007).

When focusing on the case fatality rate in the different age-groups, it can be seen in Figure 8, that fatal cases of MARF are present in all age-groups. A subgroup-analysis turned out difficult as the number of MARF cases in the very young and very old is too small for statistical analysis (Table 10). With the hypothesis, that older age might be a risk factor for MARF case fatality because of the reduced physical recovery potential associated with ageing, two age-groups were formed with a cut-off at 40 years. Even so the percentage of patients surviving MARF is lower in the age-group above 40 years (63.2% vs. 77.2%), no statistically significance between the two groups is visible (Table 10). In an Indian study conducted in an ICU setting and covering 301 severe malaria cases it has been shown however, that an age over 45 years is strongly associate with a higher frequency of fatal outcomes (Krishnan and Karnad, 2003). It can be speculated, whether there would be an observable statistically significant difference in case fatality between the different age-groups of our cases (especially in the very young and very old patients) if a bigger sample size could be obtained.

Analysing the gender and ethnicity related outcome, no statistically significance was observed concerning the relation of gender or ethnicity and case fatality (Table 11). Even though not statistically significant the Burmese MARF patients showed a higher case fatality rate than the Thai MARF patients (29.2% vs. 21.4%). In analogy to the interpretation of the higher number of Burmese patients among the MARF patients in this study (see above) this finding could be interpreted accordingly.

The analysis of the onset of the first clinical symptoms of malaria prior to admission in relation to ethnicity was done under the same hypothetical assumption as the investigation of the case fatality in the different ethnic groups (see above). The lack of statistical evidence for differences among the ethnic groups (Table 12) has the same limitation as already discussed above (incomplete data about the length of hospitalization before referral in the case of referred patients) and might not reflect the true picture. Statistical significance might be obtainable with a bigger sample size and more reliable information about the time span between first onset of clinical symptoms and initiation of treatment.

In the fatal MARF cases a subgroup-analysis has been carried out to determine the particular time of death in relation to the time of admission. The hypothetical assumption is that MARF patients can be classified in three categories:

1. Not curable, fatal even with RRT
2. Curable, but RRT is necessary
3. Curable without RRT

In the earlier mentioned Bangkok study on MARF-treatment by haemodialysis the majority of deaths occurred within 24 hours of starting haemodialysis or even before RRT was started (Wilairatana et al., 1999). This observation would support the assumption that patients who die rapidly after admission despite the immediate initiation of RRT are already in a stage of disease where even sophisticate ICU management is not able to allow the patient's survival. Again two questions arise from this assumption: What clinical and paraclinical parameters can define patients to belong to this "doomed" group of patients and what is the definite time window in which death will occur in this group ? When looking on the data of our MARF cases (Figure 9) it can be seen, that only 4 fatal cases (20%) died within the time-window of the first 24 hours after admission. But when we look on the amount of patients dying within the first 48 hours after admission the picture changes: 11 patients (55%) fall in this category. The question whether the fate of these patients is inevitable - regardless of RRT - or not is difficult to answer: Most patients die with multi-organ-failure, making it difficult to determine the role of individual factors such as MARF. On the other hand only 4 cases among the 11 patients who died within the first 48 hours received RRT.

It is quite likely, that there is a fraction of "doomed" MARF patients, who present too late in the course of their disease and who can not even be saved with immediate RRT and intensive medical care. However the retrospective design of this study and the limited amount of cases is not allowing a detailed analysis of this group. In a prospective study with a larger sample size, standardised diagnostic evaluations and treatment regimens, it might be more eligible to identify this group.

Fatal cases who were not treated with RRT

To clarify the reasons for omission of dialysis in the fatal cases not treated with RRT it has been tried to give a descriptive impression of the patients' condition, complications, prominent paraclinical abnormalities and referral background (if available) (Figure 9). The omission of RRT in these cases can be attributed to many factors (sometimes even overlapping): the limited time-window from admission to death (Patient 1, 2, 3, 7), the failure of insertion a dialysis catheter (Patient 5, 9) or clotting abnormalities and low platelets forbidding catheterization of central venous vessels (Patient 2, 3, 5, 9, 11, 12) to name the most prominent. In none of the cases death can be solely or directly attributed to MARF or the omission of RRT, but some of these cases might have benefited or even survived if RRT would have been applied.

6. Analysis of clinical symptoms, complications, therapeutical interventions and laboratory parameters as putative risk factors for death, the need for RRT and the outcome of RRT

To ease the discussion of the different putative risk factors for the different investigated outcomes of MARF the parameters have been grouped if they are possibly related to each other or show a significant association.

One drawback to be kept in mind is that the evaluated laboratory parameters as well as the patient's presenting symptoms at admission are representing the patient's condition at admission, while the WHO-criteria were cumulatively collected over the whole time of the patient's hospitalisation.

Renal failure presenting time and classification

The previously published finding that MARF is often already present at admission can be confirmed by the findings of this study (Singhal et al., 1997; Elsheikha and Sheashaa, 2007): 90.8% of the investigated MARF cases presented with established RF at admission (Table 16). This high figure might primarily reflect the account of Mae Sot General Hospital as a referral center for MARF cases and it can be speculated, whether the presence of MARF on admission is lower at the community hospital level. No statistically significant difference is observed when comparing the outcome of the MARF patients presenting with RF on admission to the MARF patients developing RF during therapy. However the power of the statistical analysis is limited by the low number of cases developing RF after hospital admission (Table 16). It could be assumed, that established RF at admission has a less favourable outcome than RF which develops during therapy as surveillance of kidney function would prompt immediate therapeutical intervention.

The renal failure classification in "oliguric", "non-oliguric" and "anuric" was aggravated by the fact, that the used classification is based on a volume over time definition, whereas the used observation time (time of admission) was a set point in time. Additionally the fluid charts were often not complete and based on 8-hour periods, making it rather difficult to judge the patient's urine-output at the time of admission. The listed frequencies and percentages in table 16 were classified as exact as possible.

In the literature different and sometimes contradictory data has been published on the amount of urine-output observed in MARF: The spectrum reaches from "often non-oliguric, but in some cases … oliguric or anuric" (Pasvol, 2005b) to "usually oliguric or anuric, rarely non-oliguric" (Trampuz et al., 2003). However most authors conclude that MARF usually presents as "oliguric and hypercatabolic" (Wilairatana et al., 1999; White, 2003a; Mishra et al., 2006; Elsheikha and Sheashaa, 2007).
In previous studies oliguric RF was found in 65.3% to 83% of the cases and non-oliguriac RF in 17% to 34.7% of the cases (Prakash et al., 1996; Wilairatana et al., 1999; Naqvi et al., 2003). Anuria is a less frequently observed feature in MARF, although reported from a Vietnamese study in 15% to 19% of the cases (Phu et al., 2002). Unfortunately the definition of anuria is not uniform among the different studies and was not available in the last mentioned publication. In our study anuria was present in 4 (6.3%), oliguria in 33 (52.4%) and non-oliguria in 26 (41.3%) cases, where data on urine-output were available (Table 16). Assuming, that directly admitted MARF cases would show more frequent anuric and oliguric RF due to uncorrected prerenal impairment when compared to referred cases - where urine-output might already has been improved by volume resuscitation - a subgroup-analysis has been carried out. However, no statistically significant difference in the frequency-distribution of anuria, oliguria and non-oliguria has been found when comparing directly admitted vs. referred cases (Data not shown).

While no statistically significant difference has been found between anuric, oliguric and non-oliguric cases and a fatal outcome or fatal outcome among the patients treated with RRT (Table 16, 18, 25 and 29) a statistically significant relationship between oligoanuric and non-oliguric cases and the need for RRT is observed (Table 17 and 27). Analysing the relationship between urine-output and the need for RRT is an interesting aspect of MARF, as urine-volume is the only accessible renal parameter in a resource-poor settings like Mae-Tao-Clinic or MSF, where kidney function tests are unavailable. Even if urine-volume is not reflection kidney function, it is a valuable parameter for guidance of fluid-management in MARF patients. Both correction of hypovolemia in the often initially existing situation of prerenal renal impairment / renal failure and the patients' disease related risk of developing pulmonary oedema and ARDS due to the increased capillary permeability observed in severe malaria is a balancing act (WHO, 2006b). Even if the voided urine volume might not largely contribute to nitrogenous waste product excretion, acid-base-balance or electrolyte homeostasis, the regulating of the patients' volume-balance is eased in non-oliguric patients. Therefore loop-diuretics are advocated and widely used to convert oliguric into non-oliguric situations, once a pre-existing volume-deficit has been corrected (White, 2003a). In a recent review concerning the use of loop-diuretics in ARF it has been concluded that loop-diuretics are not associated with improved mortality or rate of independence from RRT, but are associated with a shorter duration of RRT and increased urine output (Bagshaw et al., 2007). The difficulty in maintaining an adequate volume-balance in anuric and oliguric situations is reflected in the statistically significant higher frequency of RRT usage in this group of patients (Table 17). Despite the low number of anuric patients it is not surprising that all four anuric patients among the studied MARF cases were treated with dialysis.

Impairment of consciousness

One of the main significant associated parameter to a fatal outcome, the need for RRT and the outcome of RRT is found to be an "Impairment of consciousness" (Table 14, 15, 22, 23 and 24). Unfortunately this parameter is retrospectively difficult to analyse and interpret as it represents a black-box of different causes.

The initial criterion for cerebral malaria as defined by the WHO in 1990 was "Unrousable coma not attributable to any other cause" (WHO, 1990). In the revised WHO-criteria from 2000 and 2006 the recommendation for recognizing cerebral malaria has been changed into the broader term "any Impairment of consciousness not attributable to any other cause and/or a Glasgow-Coma-Scale (GCS) equal or less than 10" (WHO, 2000; WHO, 2006c). The "Impairment of consciousness" found among the patients covered in this study could be attributed to many reasons: High fever, electrolyte disturbances, hypoglycaemia, metabolic acidosis, sepsis, uraemia, hepatic encephalopathy, the use of sedative drugs prior to admission in the cases referred from other health institutions (difficult to judge as the referral notes are mostly not very conclusive about prior treatment measures), coexisting CNS-infections or cerebral malaria. Retrospectively an exact cause of the "Impairment of consciousness" is difficult to determine and - in the presence of various underlying factors - the impact of the individual factors is impossible to judge. In the subgroup-analysis "GCS ≤ 10" at least the cases were the "Impairment of consciousness" can be attributed to high fever alone can be excluded. Unfortunately no information is available on the improvement of the "impairment of consciousness" after dialysis in the cases treated with RRT. A marked improvement of the consciousness level after RRT would favour causes like uraemia, as cerebral malaria is not responding to dialysis therapy. Due to the fact, that cerebral malaria and MARF show different pathophysiological features and present independent from each other (Nacher et al., 2001b), it would be interesting to separate the MARF cases with coexisting cerebral malaria from the MARF cases without cerebral malaria and conduct further investigations on the impact of uraemia and other factors in the MARF associated "Impairment of consciousness".

Mechanical ventilation / Pulmonary oedema & ARDS

The need for intubation and "Mechanical ventilation" shows a statistically significant association to a fatal outcome, the need for RRT and the outcome of RRT (Table 16, 17 and 18). The most common causes for respiratory insufficiency demanding mechanical ventilation in severe malaria are pulmonary oedema and ARDS. Both complications are known for their high case fatality rates (WHO, 2006b). While pulmonary oedema is often associated with fluid overload due to concomitant ARF or improper fluid management, ARDS has been observed in patients with normal or negative fluid balance (Mishra et al., 2006). Unfortunately the collected data concerning the pulmonary complications among our 76 MARF patients is not differentiating between the entities pulmonary oedema, ALI and ARDS as radiological information were scanty and Horowitz-Indices not available. Concerning the two parameters "Mechanical ventilation" and "Pulmonary oedema / ARDS" it is found, that both are statistically significant related to each other (p-value = 0.042; Table not shown). Due to the poor data situation no causative analysis was possible by identifying patients where respiratory insufficiency led to the need for mechanical ventilation compared to cases where mechanical ventilation was at least partly involved in the development of ARDS. When we look on the statistically significant relationship between the presence of "Pulmonary oedema / ARDS" and the need for RRT (Table 17) and on the overview of complications present at the time of RRT initiation in the dialysed patients (Figure 10), it can be seen that fluid-overload is a major contributing indication for dialysis. When looking on causative correlations it is found that 9 of the 11 patients presenting with pulmonary oedema had concomitant anuria or oliguria (Figure 10; Data of subgroup-analysis not shown).

Circulatory collapse / Inotropic drugs

The presence of "Circulatory failure" has been determined according to the currently used WHO-criteria for severe malaria shown in table 1 (WHO, 2006b). The putative risk factors "Circulatory failure" and usage of "Inotropic drugs" are almost identical, as 28 of the 30 patients presenting with "Circulatory failure" are treated with "Inotropic drugs" (Table 22; Subgroup-analysis not shown). The impact of "Circulatory failure" on outcome is not surprising and therefore not further discussed. The widely used practice of FFP substitution in patients presenting "Circulatory failure" is discussed below.

Serum protein levels and transfusion of blood products

When analysing the frequency distribution of blood-component transfusions related to the outcome survival and death it can be observed, that only the transfusion of FFP has a statistically significant association with a fatal outcome (Table 16). While the transfusion of FFP in severe malaria is very rarely indicating the attempt of treating clotting abnormalities, it is a widely used measure to counteract circulatory disturbance and failure. This policy is reflected in the fact that patients treated with inotropic drugs due to circulatory collapse also received statistically significant more FFP transfusions (Table 19). The rational behind this strategy is to maintain a sufficient intravascular volume by increasing the oncotic pressure. Nevertheless the rational of this practice is controversial and even doubtful. While not much data is available on the usage of FFP, controversial data has been published concerning the usage of albumin - which is used following the same fundamental idea - in critically ill patients. Albumin is considered superior in the particular situation of ARF as all three available artificial colloids (HES [hydroxyethyl starch], gelatin and dextran) exhibited troublesome renal side-effects, whereas the normal endogenous colloid, albumin is supposed to be rather safe (Davidson, 2006). While one recent study claimed that albumin administration can improve organ function in critically ill hypoalbuminemic patients (Dubois et al., 2006) a recent review of 32 trials concluded, that there is no evidence that albumin reduces mortality in critically ill patients with burns, hypovolemia or hypoalbuminaemia (Liberati et al., 2006).

When we look on the laboratory values of our 76 MARF patients there is neither a statistically significant difference observable in the albumin level between the fatal cases and the survivors nor between the cases treated with or without RRT (Table 25 and 27). The same observation applies for the outcome of RRT (Table 29).

An interesting aspect beyond the question of albumin substitution is the impact of the other protein-fractions which are contained in FFP. Among our 76 studied MARF cases the overall survivors (Table 25) as well as the fraction of RRT-survivors (Table 29) showed a statistically significant higher globulin level than the fatal cases. As serum electrophoresis data is not available for our patients no statement can be given regarding possible differences among the globulin-fractions. A possible benefit of FFP transfusion in severe shock syndromes has been postulated by Nohé et al., who concluded, that FFP can attenuate the inflammatory response of endothelial cells as well as microcirculatory disturbance by reducing leukocyte adhesion to endothelial cells (Nohe et al., 2003). As both pathological features are discussed in MARF (see literature review above) it could be speculated whether there is a link between these observations and the lower globulin levels found in the fatal cases (Table 25 and 29). Indirect support for the assumption of a existing correlation between serum globulin level and outcome is coming from a Malaysian publication on ARF in severe malaria: Low serum globulin levels were statistically significant associated with the development of MARF, while serum albumin levels showed no such association. Unfortunately no data is available about the plasma protein levels among the subgroup of patients with MARF in that study (Koh et al., 2006).

It would be interesting to undertake further studies concerning the impact of the different plasma globulin-fractions on the outcome of MARF and possibly determine a rational benefit of FFP transfusions in this group of persons.

Another interesting and already for a long time debated issue is the impact of blood product transfusions on the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)(Popovsky, 2001; Gajic and Moore, 2005; Higgins et al., 2007). In a recent published study investigating the effect of RBC, FFP and platelet transfusions on the development of ALI and ARDS it has been found, that *any* transfusion and in particular the transfusion of plasma-rich blood products - such as platelets and FFP - is associated with the development of ALI and ARDS (Khan et al., 2007). Unfortunately the collected data concerning the pulmonary complications among our 76 MARF patients is not differentiating between the entities pulmonary oedema, ALI and ARDS as radiological information were scanty and Horowitz-Indices not available. Secondly we did not collect the data to allow a chronological correlation of FFP transfusions to the diagnosis of "ARDS / Pulmonary oedema" and thirdly no statement concerning ARDS due to nosocomial infections / respirator-associated pneumonias can be made, as information on microbiological work-up (if done) is scanty. Despite these limitations it has been tried to look for associations between the outcome "ARDS / Pulmonary oedema" and FFP transfusions: Even though no statistically significant association between "ARDS / Pulmonary oedema" and FFP transfusions is found in our study, there is a much higher percentage of "ARDS / Pulmonary oedema" in the patients receiving FFP compared to patients not receiving FFP (36.8 vs. 18.2%)(Table 20). Whether this tendency would become statistically significant in a larger study population is an interesting question. Adding the transfusion related risk to the already increased malaria related risk of developing pulmonary oedema and ARDS due to the increased capillary permeability observed in severe malaria (WHO, 2006b) the widely used generous transfusion of FFP clearly deserves more attention and further investigation to determine and evaluate potential benefit and risk. The currently applied WHO regional guidelines for the management of severe malaria in South-East Asia do not mention FFP transfusion as a treatment option for circulatory collapse (WHO, 2006a; WHO, 2006b).

Even though the transfusion of RBC was more frequently observed in the fatal cases (28.6% vs. 22.2%) no statistically significant association is found between the transfusion of RBC and the outcome survival or death (Table 16). When looking on the outcome of the dialysed patient, again no statistically significant difference is found concerning the frequency of RBC transfusion (Table 18). This observation is conform to the almost identical haemoglobin levels (Hb), haematocrit values (Hct) and RBC counts found among the different outcome groups (Table 25 and 29). It should be noted here, that the WHO-criterion "Severe anemia" was a rare finding and only present in 3 of the 76 studied cases (Table 22). When focusing on the use of RRT and the transfusion frequency of RBC, the dialysed patients show a statistically significant higher transfusion frequency compared to the non-dialysed patients (Table 17) despite almost identical baseline laboratory values of Hb, Hkt and RBC in both groups (Table 27). This could be explained by the fact that the procedure of haemodialysis itself leads to a loss of circulating blood volume by deposition of blood in the dialyser’s membrane system and lines. This loss of blood seems to be compensated by transfusion as visible in the higher transfusion frequencies observed in the dialysed patients (Table 17).

The hypercatabolic state

As mentioned above the most common manifestation attributed to MARF is a "oliguric and hypercatabolic" state. Therefore the studied MARF cases were classified according to the WHO criteria for the presence or absence of a hypercatabolic state (see appendix) and analysed for differences in outcome.

Although the analysis did not reveal a statistical significant relationship between hypercatabolism and a fatal outcome, there is a considerably higher case fatality rate found among the cases presenting a hypercatabolic state (25.6%) than among the cases not showing hypercatabolism (10.5%) (Table 16).

A strong statistically significant relationship is found between the presence of a hypercatabolic state and the use / need for RRT (Table 17). This link is not surprising, as hypercatabolism is considered to be one of the main indications for dialysis (WHO, 2006b). In fact all patients treated with RRT in our study showed a hypercatabolic state (Table 18).

Additionally a cross-tabulation of the presence and absence of a hypercatabolic state shows statistically significant relations to a decreased urine-output, the need for mechanical ventilation and the need for inotropic drugs (Table 21). That a decreased or even ceased urine-output facilitates the rise of nitrous waste products is a known causative relation. This rise of retention parameters can be very rapid in case of a concomitant hypercatabolic metabolic situation. Therefore the monitoring of urine-output and laboratory parameters reflecting hypercatabolism is of central importance in MARF patients. Concerning the need for mechanical ventilation and inotropic drugs it is clearly visible from our data that MARF patients presenting with a hypercatabolic state (67.2%) have a much higher demand for intensive medical care than non-hypercatabolic patients (90.5% vs. 36.2%)(Table 16 and21).

In summary the hypercatabolic state might not only be a good predictor for the need of RRT but also for the need of other intensive medical care facilities. Therefore laboratory parameters reflecting the hypercatabolic state might be valuable indicators for severity and fast deterioration of the patient's situation and be useful for health institutions with limited facilities - like district hospitals - to decide about the patient's referral.

BUN / Creatinine / Serum bicarbonate / Potassium

When we look on the individual parameters used to assess a hypercatabolic state (Serum bicarbonate, acidosis, BUN, creatinine and potassium [see appendix]) and their individual relationships to the investigated outcomes, a complex picture is unfolding: While BUN and creatinine levels do not show any statistically significant relation to any outcome (Table 25, 27 and 29), none of the parameters used for defining hypercatabolism is found to be statistically significant related to RRT (Table 27). Despite not showing a statistically significant relation to the need for RRT the parameters metabolic acidosis and bicarbonate level are statistically significant related to a fatal outcome and the outcome of RRT (Table 22, 24 and 31). For the potassium level it is similar: serum potassium levels do not show statistically significant relations to the need for RRT, but a fatal outcome is seen mainly in patients with higher serum potassium levels (Table 29).

How can this be explained ? Shouldn't the parameters defining the hypercatabolic state show the same relations as the hypercatabolic state ?

To answer these questions we have to consider the time the individual parameters reflect: The parameters BUN, creatinine, potassium and bicarbonate are representing a snap-shot, collected as baseline laboratory at the time of the patient's admission at the hospital. For the definition of a hypercatabolic state the changes of these parameters over time is assessed (see appendix).

In conclusion these findings imply that for the prediction of the necessity for RRT the dynamic changes of retention parameters and acid-base balance - as defined by the hypercatabolic state - are superior to static laboratory parameters. Therefore frequent monitoring of these parameters is of pivotal importance.

Concerning the acidosis found among our cases a calculation of the anion gap revealed the presence of a high anion gap suggestive of lactate acidosis. As no statistically significant difference was found when comparing the anion gap of the different investigated outcome groups, the etiopathogenesis of the acidosis is probably not differing in causative mechanisms among the different groups.

WBC count

Among the haematological parameters only the "WBC count" showed a statistically significant relationship to the different investigated outcomes. Statistical significance is found among all analysed outcomes: high WBC counts are related to a higher frequency of fatal outcomes, a higher demand for RRT and a higher case fatality rate among patients treated with dialysis (Table 25, 27 and 29). The higher WBC count among these cases might indicate secondary infection aggravating the patient's condition, enhancing the requirement for RRT and diminishing the survival chances.

When looking on the neutrophil and lymphocyte count, there seems to be - although not statistically significant - a tendency to higher neutrophil counts and lower lymphocyte counts in the fatal cases. These findings would support the hypothetical assumed higher frequency of bacterial superinfections in the fatal cases. The impact of secondary bacterial infection should not be underestimated considering that the three most common complications leading to death in adults Thai patients with severe malaria were reported to be pulmonary oedema, MARF and sepsis (Wilairatana et al., 1999). Unfortunately the only infrequently conducted and low yield microbiological work-up of the cases covered in this study is not sufficient to allow an analysis of the most prevalent pathogens complicating MARF. Bacterial superinfection and sepsis (especially due to gram-negative bacteria) in patients with severe malaria is a known complication, prompting the WHO to recommend the empirical administration of broad-spectrum antibiotics (e.g. third-generation cephalosporins) in patients presenting with circulatory collapse (WHO, 2006b).

Empirical antibiotic treatment (in the form of Ceftriaxone) was given to 48 of the 76 MARF cases (63.2%) [no further discussion will be carried out concerning the frequently used combination of 2 or more antibiotics found in 33.3% of the cases] (Data not displayed). Considering the WHO recommendation of empirically giving broad-spectrum antibiotics to patients with circulatory collapse in order to cover gram-negative sepsis a closer look was taken on the antimicrobial treatment of this subgroup: Among the 30 patients presenting circulatory collapse only 20 (66.7%) were treated with antibiotics (Table 22; Subgroup-analysis not shown). This low figure suggests that more adherence to the current treatment guidelines recommended by the WHO should be promoted and enforced.

Jaundice / Hepatomegaly / AST / ALT

Among the complications associated with severe malaria "Jaundice" / "Hyperbilirubinaemia" was found to be linked to the development of ARF (Mukherjee et al., 1971; Sitprija et al., 1977; MacPherson et al., 1985; Wilairatana et al., 1994; Nacher et al., 2001b). While the general concept of the relationship between jaundice / hyperbilirubinaemia and MARF is widely accepted, no study has been conducted concerning the impact of jaundice / hyperbilirubinaemia on the outcome of MARF.

Jaundice in malaria has a multifactorial etiopathogenesis including malarial hepatitis / hepatocellular dysfunction, intrahepatic cholestasis, intra- and extravascular haemolysis of PRBC and disseminated intravascular coagulation (DIC) to name the most prominent features (Anand and Puri, 2005). The question which mechanism and what parameter has the highest impact on renal function is still unclear. In a study carried out in Thailand, it has been shown that in addition to hyperbilirubinaemia, hepatomegaly is associated with MARF (Nacher et al., 2001b).

Among our 76 MARF cases the presence of jaundice or the level of hyperbilirubinaemia did not show any statistically significant relation to the investigated outcomes death, RRT or the outcome of RRT (Tables 22, 23, 24, 25, 27 and 29). Although not significant it seems that a slightly higher bilirubin level is found among the patients in the need for RRT (Table 29). Concerning the overall outcome and the outcome of patients treated with dialysis a converse relation seems to exist: although not statistically significant the survivors seem to have higher bilirubin levels than the fatal cases (Total bilirubin: 11.1mg% [0.4 - 30.1] vs. 4.95mg% [1.9 - 32.5]; Direct bilirubin: 3.4mg% [0.1 - 93.0] vs. 1.7mg% [0.6 - 12.8]) (Table 25). A similar picture is found among the survivors and fatal cases treated with RRT (Total bilirubin: 13.3mg% [1.1 - 30.1] vs. 5.4mg% [2.4 - 32.5]; Direct bilirubin 4.4mg% [0.4 - 10.4] vs. 1.8 [0.8 - 11.3]) (Table 29). The interpretation of these findings is unclear, especially as no marked difference in the proportion of direct over indirect bilirubin in the different groups can be observed, suggesting that no major difference in the underlying ethiopathogenesis of hyperbilirubinaemia is present. With direct and indirect bilirubin raised both hepatic dysfunction - leading to impaired bilirubin excretion - and haemolysis seems to contribute to the raised serum levels.

The relevance of hyperbilirubinaemia in severe malaria appears to be complex: In an Indian study focusing on the impact of hyperbilirubinaemia on malaria-related mortality 1103 patients with falciparum malaria have been studied: 64.3% of the subjects were hyperbilirubinemic. Hyperbilirubinemic patients were more likely to have cerebral malaria (24.1% *v.* 9.4%; $p < 0.0001$) and MARF (9.5% *v.* 2.3%; $p < 0.0001$). The mortality rate was 7.9% among the patients with hyperbilirubinaemia (all the deaths being attributable to cerebral malaria, acute renal failure and/or severe anaemia) but only 1% among the non-hyperbilirubinemics. There were no deaths, however, among the 506 hyperbilirubinemic patients who did not have cerebral malaria, ARF or severe anaemia (even among those with high serum bilirubin concentrations). It therefore appears that in falciparum malaria, hyperbilirubinaemia itself is not a severe complication, and only appears to be linked with mortality when associated with at least one other complication (Mishra et al., 2004). This is the reason why - according to the current WHO-criteria - hyperbilirubinaemia / jaundice is only considered as a sign of severe malaria in combination with evidence of another vital organ dysfunction (WHO, 2006b). When considering the findings of our study were all patients had at least MARF as concomitant complication the impact of hyperbilirubinaemia on mortality is still far from clear.

The clinical finding of "Hepatomegaly" - present at the time of the patient’s admission - was statistically significant associated with a fatal outcome among our studied patients (Table 14). This observation is backed up by the laboratory findings, showing statistically significant higher AST and ALT levels among these patients (Table 25).

In addition to hyperbilirubinaemia, hepatomegaly and high Aspartat-aminotransferase (AST) levels have been described as being associated with the development of MARF in previous studies (Wilairatana et al., 1999; Barsoum, 2000; Nacher et al., 2001b). No published data, however has been found on the impact of these factors on the outcome of MARF. In this study 35.3% of the MARF cases presented with hepatomegaly. Even so the definition of hepatomegaly can not be retrospectively evaluated (in most cases the physician in charge was simply recording the finding "Hepatomegaly" in the patient’s chart without specifying the palpable liver size) a similar figure of 45% was described among Vietnamese MARF cases, and in a Thai study, where a palpable liver of more than 2 cm below the right costal margin was present in 40% of the studied MARF cases (Nacher et al., 2001b).

Hepatic dysfunction in severe malaria infection is a long known and well described entity, with a abundance of assumed factors. Despite the commonly used term "Malarial hepatitis" in malaria associated hepatocytic dysfunction, inflammation of the liver parenchyma is almost never seen (Anand and Puri, 2005). The proposed underlying pathogenesis include micro-occlusion of portal venous branches by parasitized red blood cells (PRBC) leading to ischemic hepatocellular damage, endotoxemia due to severe systemic infection, intrahepatic cholestasis due to reticuloendothelial blockage and hepatic microvilli dysfunction (Aung et al., 1988;

Molyneux et al., 1989; White, 2003a; Anand and Puri, 2005). The presence of hepatitis in severe malaria indicates a more severe illness with a higher incidence of complications and a poorer prognosis (Bhalla et al., 2006). In a study conducted in India malarial hepatitis showed a higher incidence of ARF (60% vs. 25%), a higher incidence of ARDS (35% vs. 3%) and a higher incidence of septicaemia (20% vs. 6%) compared to patient without hepatitis. The overall mortality observed in this particular study was notedly higher in patients with malarial hepatitis (40% vs. 17%)(Murthy et al., 1998). The occurrence of acute liver failure, hepatic encephalopathy or coagulopathies are considered exceptional findings and hepatic function seems to be not altered by "Malarial hepatitis" as clotting times are usually normal even in patients with marked elevation of liver enzymes (Bhalla et al., 2006). This reported data are consistent with the findings of our study. Although the clotting times (PT, PTT and INR) are slightly increased and the albumin level is slightly decreases among the fatal cases when compared to the surviving cases, statistical significance between the two groups is missing (Table 25).

Patients with the need for RRT showed statistically significant higher AST levels when compared to non-dialysed patients (Table 27). Among the dialysed patients a statistically significant higher AST level - and a statistical tendency towards a higher ALT level - is found among the fatal cases (Table 29).

Concerning the hepatic findings in our 76 studied cases it can be concluded, that "Jaundice / Hyperbilirubinaemia" has no statistically significant predictive value for the outcome of MARF, while "Hepatomegaly" and raised "Transaminase levels" show a statistically significant value as predictive factors for survival and death. Therefore the presence of hepatomegaly and raised transaminase levels might be - in combination with other findings - helpful parameters in a district hospital setting when considering a patient’s referral.

Urine specific gravity / Urine RBC

The relation of the "Urine specific gravity" to the different investigated outcomes has to be seen critically. As this laboratory value is only reflecting the time of the patient’s admission, the only conclusion which can probably be derived from this parameter is the degree of prerenal impairment the patient is presenting at the time of admission. The response to volume resuscitation and / or inotropic drugs after admission is not reflected by these figures. As a statistical tendency to higher urine specific gravity values is observed among all groups with a less favourable outcome this might just point towards a higher degree of prerenal impairment / failure at admission (Table 25, 27 and 29).

The interpretation of the statistically significant higher number of "Urine RBC" found among the patients treated with RRT is difficult and might be iatrogenic caused by urethral catheterization (Table 27). This procedure is probably more often carried out - or even supposed to be an obligatory standard procedure - in patients receiving RRT. Unfortunately corresponding data have not been collected to proof this assumed relationship. Another possibility would be that the higher amount of urine RBC found among the patients with need for RRT is reflecting underlying glomerulonephritis. When we look on the amount of proteinuria between the patients receiving RRT and the ones not receiving RRT - although not significant - a statistically tendency towards a higher degree of proteinuria is found among the dialysed patients (Table 29). However renal biopsy would be necessary to investigate glomerulonephritis.

Chloride / Sodium / Potassium

Statistically significant differences are found concerning the serum electrolyte composition of fatal cases and survivors in the group of patients treated with RRT (Table 29). Statistically lower sodium and chloride levels and higher potassium levels are observed among the patients who died.

The etiopathogenesis of these electrolyte displacements could be explained as follows: Hyperkalaemia is a commonly found complication in ARF and one of the classical indications for RRT. The accumulation of potassium in ARF is attributed to acidosis (shifting potassium out of cells) and impaired renal excretion of potassium (Cumming, 2002). In MARF patients haemolysis might contribute to the rising potassium levels as well. The degree of serum potassium increment is reflecting the degree of severity of the underlying kidney malfunction with rapid changes in potassium levels over time being a good indicator for the presence of a hypercatabolic state (see above)(WHO, 2006b). The higher level of hyperkalaemia found in the fatal

RRT cases might therefore indicate a more severe degree of acidosis, haemolysis and renal dysfunction.

The low serum chloride and sodium levels can be explained by diminished renal re-absorption of these soluble due to kidney dysfunction. Reduced re-absorption is a consequence of acute necrosis of the responsible tubular epithelium cells which is considered the hallmark of MARF (see above). Besides acute tubular necrosis (ATN) dysfunction of tubular epithelium cells might play a role as well: In a recent study it has been shown that pro-inflammatory cytokines can cause down-regulation of renal chloride entry pathways in patients with sepsis (Schmidt et al., 2007). It can be speculated whether similar mechanisms are present in severe malaria infections.

Again we have to bear in mind, that the electrolyte levels are reflecting the baseline laboratory (iatrogenic dilution effects due to prior fluid resuscitation might be involved in the referred cases). Therefore it might be assumed that patients presenting this pattern of electrolyte displacements at admission have a very high risk of dying despite dialysis. This assumption brings us back to the earlier speculation concerning the existence of a "doomed" group of MARF patients who present too late in the course of their disease and who can maybe not even be saved with immediate RRT and ICU-care (see above). These electrolyte displacements might be potential predictive factors to identify this group of patients.

Complication present at the time of initiating RRT

When it comes to the question "What were the indications for initiating RRT in the studied MARF cases ?" it becomes difficult again: the exact complications prompting the physician in charge to start dialysis are retrospectively difficult to determine, as notes in the patients' files in this regard are scarce or absent. Therefore it has been tried to identify the most probable influencing factors by analysing the available laboratory data at the time of the initiation of RRT: It is found, that "Anuria / Oliguria", "Acidosis" and a "Hypercatabolic state" are the three most important RRT-indications among MARF patients. It is also found that in most cases considerable overlap between these RRT-indications is observed (Figure 10). An interesting aspect of the subgroup-analysis concerning the presence of the different RRT-indications in relationship to the outcome survival and death is, that none of the patients presenting only 1 of these 3 RRT-indications died, while 2 fatal cases are found among the 13 patients presenting with 2 RRT-indications (15.4%) and 6 fatal cases are found among the 15 patients presenting the 3 RRT-indications (40%) (Figure 10; Data of outcome analysis not shown). These figures suggest a direct association between the number of complications present at the time of starting RRT and case fatality.

Starting RRT is mostly a decision influenced by multiple factors including laboratory values and clinical symptoms. All of the studied cases showed two or more of the 5 different found complications when RRT was started (Figure 10). Weighing the individual factors on their influence on starting RRT is retrospectively not possible and probably even prospectively a challenge.

7. Logistic regression analysis of the identified statistically significant associated putative risk factors in relationship to the different outcomes

The logistic regression analysis of the collected data was hampered by the large amount of missing data: With only 38 (50%) of the collected cases included in the analysis of survival and death in MARF, 19 cases (25%) included in the analysis for the need of RRT and only 10 eligible cases (13.2%) in the analysis concerning the outcome of RRT, the power of this analysis was considerably low. However when looking on the rather meagre result of the logistic regression analysis, one aspect sticks out and might deserve further attention and studying: the serum globulin level. So far not much attention was been paid to this parameter, but when we look on the data of this study (and the limited observational data found by reviewing existing publications), this parameter might not only show to be valuable predictive factor for assessing the outcome of MARF, but might also be a potential starting point to consider new treatment options.

8. The observed baseline-characteristics, dialysis-frequencies, dialysis-durations and outcomes of the different RRT modalities among the studied MARF patients.

Even though a detailed analysis concerning the different RRT modalities is not possible, it might be interesting to look on the available data concerning the needed frequency and duration of RRT in MARF. Unfortunately it was not possible to find published data about the needed frequency and duration of PD in MARF. Available data on frequencies and durations of HD in MARF has been found in two published studies:

In the already mentioned study conducted at the Hospital for Tropical Diseases in Bangkok 101 out of 112 MARF cases (90.2%) were treated with haemodialysis with a median of 6.5 cycles (Range: 1 - 27) and a median duration of 9.7 days (Range: 1 - 41) resulting in an overall case fatality rate of 10.7% (Wilairatana et al., 1999). In the 2nd published study from Pakistan 99 out of 124 MARF cases (79.8%) were treated with haemodialysis with a median of 6 cycles (Range: 2 - 21) [data about the duration of RRT were not obtainable] resulting in an overall case fatality rate of 26% (Naqvi et al., 2003).

32 (42.1%) of our 76 MARF patients received RRT: 16 patients were treated with HD, 10 patients with PD and 6 patients received PD and HD (Table 16). The MARF patients treated successfully with HD in our study received a median of 2.5 cycles (1 - 9) applied over a median time of 8 days (Range: 1 - 13) [Note: The cases treated with HD and PD are not included in these figures]. Even so the comparison of our data to the above mentioned studies concerning frequency and duration of HD is rather crude - as indications and baseline characteristics among the cases might be very different - there are some interesting aspects: The above displayed studies included the fatal cases in their figures. As most fatal cases occurred within the first 24 hours (Wilairatana et al., 1999) or 48 hours (Naqvi et al., 2003) the overall median HD frequencies and durations given above are probably reflecting lower numbers than what would be found when looking on the HD frequencies and durations of the surviving patients alone. It is interesting, that even if we look on the overall medians of the applied HD cycles and durations in these studies, we find a far lower requirement for dialysis

frequency and duration in our patients. This finding could imply that the needed frequency and duration of RRT in MARF might be far lower than what is assumed from the published data. A prospective study would be interesting and necessary to determine how much RRT is really necessary in patients with MARF.

9. The frequency distribution of complications present at time of death

The frequency distribution of complications present at the time of death among the 20 fatal MARF cases is shown in Figure 15. Due to the retrospective study design and the fact, that in many cases the exact presence of the different complications was not always documented by the physician in charge, the presented figure tries to provide a merely descriptive - as accurate as possible - frequency distribution reconstructed from the files. What is clearly visible from the available data is the fact that a large majority of the fatal cases is dying with multi-organ-failure. In fact none of the patients among the 20 fatal cases had less than 2 organ failures involved when dying. This finding is conform with the results of a study concerning the incidence and severity of multiple-organ-dysfunction in severe malaria conducted in India, where it has been shown, that the case fatality rate is highly associated with the number of failing organs involved (Krishnan and Karnad, 2003).

10. The outlier

There are two "outliners" among the 76 investigated MARF cases: interestingly not only in the way of presentation, but also concerning the age of the affected patients.

Severe vivax malaria

Among the 76 investigated MARF cases 75 were caused by *P. falciparum*. Only one case of MARF was due to *P. vivax* infection. In general severe manifestations of malaria associated with *P. vivax* are rare, but well known. Among the complications reported in *P. vivax* infections ARF (Prakash et al., 2003; Kaur et al., 2007) cerebral malaria (Verma and Magotra, 1976; Sachdev and Mohan, 1985; Arora et al., 1988; Beg et al., 2002; Ozen et al., 2006; Thapa et al., 2007), pulmonary oedema / ARDS (Munteis et al., 1997; Pukrittayakamee et al., 1998; Illamperuma and Allen, 2007), liver involvement (Mohapatra et al., 2002; Barcus et al., 2007), splenic rupture (Gockel et al., 2006), hyperparasitemia and acidosis (Barcus et al., 2007) are described in the literature.

The *P. vivax* associated MARF case in this study was interestingly the oldest patient included in the study (74 years). Unfortunately no data was obtainable about any underlying chronic disease which could have aggravated the malaria infection - a not unreasonable suspicion in this age. In addition to MARF the patient also showed metabolic acidosis and some degree of impaired consciousness (not further specified or classified by a GCS score). The patient was treated with a course of Chloroquine, had no need for RRT or other intensive care measures and was discharged after recovering.

Exchange transfusion

The youngest patient included in this study is a 4 year old child which presented with ARF (Creatinine 3mg%, BUN 81mg%), circulatory collapse, severe metabolic acidosis (serum pH 6.9) and hypoglycemia. Even though data about the degree of parasitema was not obtainable from the patient's file hyperparasitemia was probably present as well, as exchange transfusion was performed. The patient died 7 hours after admission.

CHAPTER VII
CONCLUSION

Malarial acute renal failure was complicating 76 of 412 severe malaria cases admitted and treated at Mae Sot General Hospital between January 1st 2002 and December 31st 2007.

The manifestation rate of MARF was 90.8% at the time of hospital admission and the overall mortality rate was found to be 26.3%. A statistically significant difference was found in case fatality rates between referred and directly admitted patients (36.8% vs. 15.8%) with the highest case fatality rate in the subgroup of patients being referred from a NGO-setting (50%).

Among the investigated parameters several putative risk factors were found to be statistically significant related to a fatal outcome, the need for RRT and the outcome of patients treated with dialysis:

An "Impairment of consciousness", a "GCS < 10", "Coma" and "Hepatomegaly" at admission as well as "Circulatory collapse", the need for "Inotropic drugs", "Mechanical ventilation", "FFP transfusions", the baseline laboratory findings of high "WBC" counts, elevated "AST" and "ALT" levels, "Metabolic acidosis", reduced "Bicarbonate" levels, reduced "Total serum protein" and "Globulin" levels were all statistically significant related to a fatal outcome among MARF patients.

An "Impairment of consciousness", a "GCS < 10" and "Anuria / Oliguria" at admission as well as "Circulatory collapse", the need for "Inotropic drugs", the presence of "Pulmonary oedema / ARDS", the need for "Mechanical ventilation", "FFP transfusions" and "RBC transfusions", the baseline laboratory findings of high "WBC" counts, elevated "AST" levels, high "Urine specific gravity" and "Urine RBC" levels were all statistically significant related to the need for RRT among MARF patients.

An "Impairment of consciousness" and a "GCS < 10" at admission as well as "Circulatory collapse", the need for "Inotropic drugs", the presence of "Pulmonary oedema / ARDS", the need for "Mechanical ventilation", "FFP transfusions", the baseline laboratory findings of high "WBC" counts, elevated "AST" levels, "Metabolic acidosis", reduced "Bicarbonate" levels, reduced "Total serum protein" and "Globulin" levels, prolonged "PTT", elevated "Potassium" and low "Sodium" and "Chloride" levels were all statistically significantly related to a fatal outcome among MARF patients treated with dialysis.

Some of these parameters might be helpful when considering a patient's referral between health facilities with different settings: besides patients with clinically manifest organ dysfunctions, referral might be considered in "Oligoanuric hypercatabolic" patients due to their increased demand for RRT and other intensive medical care (mechanical ventilation and circulatory support by inotropic drugs). Additionally patients with evidence of "Malarial hepatitis" ("Hepatomegaly" and high "AST" levels), high "WBC" counts, severe "Acidosis" and low serum "Total protein" and "Globulin" levels might benefit from early referral. High serum "Potassium" levels in combination with low "Sodium" and "Chloride" levels and prolonged "PTT" at admission might identify MARF patients who present too late in the course of their disease and who can not even be saved with rapid RRT and intensive medical care.

32 (42.1%) of the 76 MARF patients received RRT (16 patients were treated with HD, 10 patients with PD and 6 patients received PD and HD). The patients successfully treated with HD in our study received a median of 2.5 cycles (1 - 9) applied over a median time of 8 days (1 - 13). This finding suggests that the needed frequency and duration of HD in MARF might be far lower than what is assumed from previous published data.

None of the patients among the 20 fatal MARF cases had less than 2 organ failures involved when dying. The majority of the fatal MARF cases died with multi-organ-failure.

Some factors and parameters influencing the outcome of MARF patients are "non-manageable" (including underlying diseases, age), others can be considered "manageable". While patients presenting with multi-organ-failure are difficult to manage even in settings where intensive care facilities and highly trained staff is available the most prominent manageable factor might be delayed treatment. Besides being possibly the strongest outcome-related factor, it also might be the most accessible factor to be influenced. Our data clearly show a strong relation between fatal outcome and referred MARF patients indicating delayed treatment. The first steps in improving the present situation might therefore focus on increasing the awareness of this factor among the medical staff in charge and considering the creation and implementation of local referral guidelines for MARF patients. Even though maybe not feasible for NGO settings, the encouragement and implementation of peritoneal dialysis at community hospital level might be a second valuable step in improving the outcome of MARF patients.

The statistically significant difference in serum "Total protein" and "Globulin" levels which is found between the survivors and fatal cases in this study clearly deserves further investigations, as it might not only be a valuable predictive factor for outcome, but also a potential starting-point for the treatment of MARF. Furthermore research concerning the impact of different plasma globulin-fractions on the outcome of MARF could help to determine a rational benefit of the widely used policy of FFP transfusions in circulatory-impaired patients and a possibly transfusion-related risk for developing ARDS.

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APPENDIX

1. The "Glasgow Coma Scale" (GCS)

The GCS, a score used to assess the neurological state of a patient, is calculated by summing up the best eye, verbal and motoric response a patient is able to perform:

(E) Best eye response

There are 4 grades starting with the most severe:

1 No eye opening
2 Eye opening in response to pain
3 Eye opening to speech
4 Eyes opening spontaneously

(V) Best verbal response

There are 5 grades starting with the most severe:

1 No verbal response
2 Incomprehensible sounds
3 Inappropriate words
4 Confused
5 Oriented

(M) Best motor response

There are 6 grades starting with the most severe:

1 No motor response
2 Extension to pain (decerebrate response: adduction, internal rotation of shoulder, pronation of forearm)
3 Flexion in response to pain (decorticate response)
4 Withdraws from pain (pulls part of body away when pinched; normal flexion)
5 Localizes to pain. (Purposeful movements towards changing painful stimuli; e.g. hand crosses mid-line and gets above clavicle when supra-orbital pressure applied)
6 Obeys commands

$$\sum_{GCS} = E_{(1-4)} + V_{(1-5)} + M_{(1-6)}$$

The GCS therefore ranges from 3 to 15 (Teasdale and Jennett, 1974).

2. The reference units and values of laboratory parameters at Mae Sot General Hospital

Parameter	Unit	Normal range
Hb	g%	
Hct	%	
RBC	x 10^2/l	4.2 – 6.3
WBC	x 10^6/l	4.5 – 10
Neutrophiles	%	
Lymphocytes	%	
Platelet-count	x 10^9/l	140 – 450
Parasite-count total	% /100 RBC	
Parasite-count total	% /200 WBC	
Schizont-count	/µl	
Trophozoite-count	/µl	
Gametozyte-count	/µl	
Creatinine	mg%	0.5 – 1.5
Uric acid	mg%	2.4 – 7
BUN	mg%	8 – 23
Serum pH	-	
HCO_3^-	mmol/l	22 – 28
Sodium	mmol/l	135 – 148
Potassium	mmol/l	3.7 – 5.3
Chloride	mmol/l	98 – 106
Calcium	mg%	8.4 – 10.4
Magnesium	mg%	1.5 – 2.5
Blood Glucose	mg%	70 – 110
Bilirubin total	mg%	0 – 1
direct Bilirubin	mg%	0 – 0.35
ASAT	U/l	5 – 40
ALAT	U/l	5 – 40
Alk. Phosphatase	U/l	35 – 125
Total Protein	g%	6 – 8
Albumin	g%	3.5 – 5
Globuline	g%	2.5 – 3.5
CPK	U/l	M < 175, F < 140
LDH	U/l	114 – 240
Urine pH	-	
Urine microalbumin	mg/dl	< 20
Urine protein	mg	30 – 200
Urine sugar	mg%	
Urine specific gravity	g/l	
Urine RBC	/HPF	
Urine WBC	/HPF	
Urine Haemoglobin	-/+	
Urine casts	/LPF	
PT	seconds	11 – 18
PTT	seconds	23 – 29
INR	-	
ESR	mm/h	0 – 15

3. Operational definition of fever clearance time (FCT)

Time (in hours) of fever after starting antimalarial treatment until oral temperature decreases to 37.5°C and remains below this temperature for ≥ 48h.

4. Operational definition of renal failure classification

Oliguria Urine output of less than 400 ml in 24 hours in adults and less than 0.5 ml per kilogram body-weight per hour in children

Anuria Cessation of urine output

5. Operational definition of the hypercatabolic state

A hypercatabolic state is defined by the presence of at least one of the following features:

- Increase of BUN > 20 mg/dl per day
- Increase of Creatinine > 1 mg/dl per day
- Increase of serum Potassium > 1 mmol/L per day
- Decrease of HCO_3 > 2 mmol/L per day

(WHO, 2006b)

6. Case record form

Patient ID No. __________ 1

Date of Admission _____/_____/_________ ____:____
DD MM YYYY HH MM

Demographic data

Date of birth_____/_____/_________ (9) No data ☐
DD MM YYYY

Gender (1) male ☐ (2) female ☐ (9) No data ☐

Ethnicity (1) Burmese ☐ (2) Thai ☐ (3) Karen ☐
(4) Hmong ☐ (5) Other ☐ (9) No data ☐
↳specify ______________

Residency Tak Province:
(1) Mae Sot district ☐ (3) Other Province: ____________ ☐
(2) Other district ☐ (9) No data ☐

Occupation (1) Farmer ☐ (2) Labour ☐ (3) Office/Government ☐
(4) Other ☐ (5) None ☐ (9) No data ☐
↳specify ______________

Past medical history

Previous malaria infection (1) No ☐ (2) Yes ☐ (9) No data ☐

History of chronic illness (1) No ☐ (2) Yes ☐ (9) No data ☐

If Yes:
(1) Hypertension ☐ ______________
(2) Diabetes mellitus ☐ ______________
(3) Kidney disease ☐ ______________
(4) Liver disease ☐ ______________
(5) Pulmo. disease ☐ ______________
(6) Heart disease ☐ ______________
(7) Neurol. disease ☐ ______________
(8) HIV positive ☐ ______________
(9) Other ☐ ______________

Long-term medication (1) No ☐ (9) No data ☐
(2) Yes ☐ Drug(s) ______________

Patient ID No. ______ 2

Presenting Symptoms (1) No ☐ (2) Yes ☐ (9) No data ☐

If Yes:

	Symptoms		Duration of illness
1	Fever	☐	
2	Chills / Rigor	☐	
3	Myalgia	☐	
4	Arthralgia	☐	
5	Fatigue	☐	
6	Anorexia	☐	
7	Vomiting	☐	
8	Abdominal discomfort	☐	
9	Diarrhoea	☐	
10	Jaundice	☐	
11	Dark urine	☐	
12	Decrease of urine volume	☐	
13	Peripheral oedema	☐	
14	Cough / Dyspnoea	☐	
15	Headache	☐	
16	Alteration of consciousness	☐	
17	Convulsion(s)	☐	
18	Coma	☐	
19	Other:	☐	
20	Other:	☐	
21	Other:	☐	

Patient ID No. ______ 3

Physical examination ____/____/______ ______:______
DD MM YYYY HH MM

(1) Jaundice	(1) No ☐	(2) Yes ☐	(9) No data ☐
(2) Anemia	(1) No ☐	(2) Yes ☐	(9) No data ☐
(3) Splenomegaly	(1) No ☐	(2) Yes ☐	(9) No data ☐
(4) Hepatomegaly	(1) No ☐	(2) Yes ☐	(9) No data ☐
(5) Peripheral oedema	(1) No ☐	(2) Yes ☐	(9) No data ☐
(6) Impaired consciousness	(1) No ☐	(2) Yes ☐	(9) No data ☐
(7) Convulsions	(1) No ☐	(2) Yes ☐	(9) No data ☐
(8) Coma	(1) No ☐	(2) Yes ☐	(9) No data ☐
(9) Other:____________________	(1) No ☐	(2) Yes ☐	(9) No data ☐

(10) Glasgow Coma Scale: Eye response ☐
Verbal response ☐
Motoric response ☐
Total ☐

Chest X-Ray (1) No ☐ (2) Yes ☐ (9) No data ☐

If Yes: ____/____/______ ______:______
DD MM YYYY HH MM

Pulmonary oedema	(1) No ☐	(2) Yes ☐	
Infiltrations	(1) No ☐	(2) Yes ☐	specify: ______________
Other	(1) No ☐	(2) Yes ☐	specify: ______________

Criteria for severe malaria other than ARF (WHO 2006)

(1) Impaired consciousness	(1) No ☐	(2) Yes ☐	(9) No data ☐
(2) Severe pallor/anemia	(1) No ☐	(2) Yes ☐	(9) No data ☐
(3) Jaundice/Hyperbilirubin.	(1) No ☐	(2) Yes ☐	(9) No data ☐
(4) Circulatory collapse	(1) No ☐	(2) Yes ☐	(9) No data ☐
(5) Metabolic acidosis	(1) No ☐	(2) Yes ☐	(9) No data ☐
(6) Pulmonary odema/ARDS	(1) No ☐	(2) Yes ☐	(9) No data ☐
(7) Multiple convulsions	(1) No ☐	(2) Yes ☐	(9) No data ☐
(8) Spontaneous bleeding	(1) No ☐	(2) Yes ☐	(9) No data ☐
(9) Hemoglobinuria	(1) No ☐	(2) Yes ☐	(9) No data ☐
(10) Hypoglycemia	(1) No ☐	(2) Yes ☐	(9) No data ☐
(11) Hyperparasitaemia	(1) No ☐	(2) Yes ☐	(9) No data ☐
(12) Prostration	(1) No ☐	(2) Yes ☐	(9) No data ☐

Patient ID No. ______ 4

Renal failure

(1) Present on admission ☐

(2) Developing during therapy ☐ ____/____/______ (DD MM YYYY)

Renal failure classification (at day before dialysis or dialysis day)

(1) Oliguric renal failure ☐ ____/____/______ (DD MM YYYY)

(2) Non-oliguric renal failure ☐ ____/____/______ (DD MM YYYY)

(3) Anuric renal failure ☐ ____/____/______ (DD MM YYYY) (9) No data ☐

Renal replacement therapy (RRT) (1) No ☐ (2) Yes ☐

If Yes: **(A) Type of RRT:**

(1) ☐ Peritoneal Dialysis starting day ____/____/______ (DD MM YYYY)

$\sum$dialysis cycles ______ ending day ____/____/______ (DD MM YYYY)

(2) ☐ Hemodialysis starting day ____/____/______ (DD MM YYYY)

$\sum$dialysis cycles ______ ending day ____/____/______ (DD MM YYYY)

Change of dialysis-type during treatment (1) No ☐ (2) Yes ☐

If yes, reason: ________________________________

(B) Initial indication for renal replacement therapy

(1) Pulmonary oedema ☐
(2) Metabolic acidosis ☐
(3) Uraemic complications ☐
(4) Hyperkalaemia ☐
(5) I.v. nutrition substitution ☐
(6) Other:____________________ ☐
(9) No data ☐

Patient ID No. ______ 5

Anti-malarial drugs Prior to admission (1) No ☐ (2) Yes ☐

If Yes, Drug: ______________________________

Anti-malarial treatment

		Start		End	
		__/__/____ DD MM YYYY	___:___ HH MM	__/__/____ DD MM YYYY	___:___ HH MM
1	Artesunate				
2	Quinine				
3	Doxycycline				
4	Tetracycline				
5	Mefloquine				
6	Other:				

Fever clearance time Duration (in hours) of fever from the start of antimalarial treatment till the patients become afebrile, i.e.,oral temperature decreases to 37.5°C and remains below this temperature for ≥ 48 hr .

Fever-end date_____/_____/_______ ___:___ FCT = _____ hours
DD MM YYYY HH MM

Mechanical Ventilation (1) No ☐ (2) Yes ☐

Intubation: _____/_____/_______ ___:___ Extubation: _____/_____/_______ ___:___
DD MM YYYY HH MM DD MM YYYY HH MM

Inotropic drugs (1) No ☐ (2) Yes ☐ specify:___________________

If Yes: maximum dose _____ µg/kg/min

Start time: _____/_____/_______ ___:___ End time: _____/_____/_______ ___:___
DD MM YYYY HH MM DD MM YYYY HH MM

Antibiotics (1) No ☐ (2) Yes ☐ If Yes: Name of Antibiotic: ______________

Microbiological findings:

Blood culture	
Urine culture	
Sputum culture	
Other:	

Transfusions (1) No ☐ (2) Yes ☐

If Yes:
Blood (1) No ☐ (2) Yes ☐ Amount: _______________
Platelets (1) No ☐ (2) Yes ☐ Amount: _______________
FFP (1) No ☐ (2) Yes ☐ Amount: _______________

Patient ID No. ______ 6

Outcome (1) Survival ☐ Date of hospital discharge _____/_____/______ (DD MM YYYY)

(2) Death ☐ Date of death _____/_____/______ ___:___ (DD MM YYYY HH MM)

If death, suspected cause(s) of death:

1	Cerebral malaria	☐
2	Renal failure	☐
3	Acidosis	☐
4	Hyperkalaemia	☐
5	Respiratory failure	☐
6	Cardiac / Circulatory failure	☐
7	Liver failure	☐
8	2^{nd}ary infection / sepsis	☐
9	Abnormal bleeding / DIC	☐
10	Multi-organ failure	☐
11	Other:	☐
99	No data	☐

Patient ID No.: __________			Day	Day	Day	Day
		Date:	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__	__/__/__ __:__
	Temperature	**°C**				
	Pulse rate	**/min**				
	Blood pressure	**mmHg**				
	Intake oral	**ml/24h**				
	Intake i.v.	**ml/24h**				
	Intake total	**ml/24h**				
	Output urine	**ml/24h**				
	Output ultrafiltration	**ml/24h**				
	Output total	**ml/24h**				
Hematology	Hb	g%				
	Hct	%				
	RBC	x 10^2/l				
	WBC	x 10^6/l				
	Neutrophil	%				
	Lymphocyte	%				
	Platelet-count	x 10^9/l				
	P.f. / P.v. / mix inf.	-				
	G6PD					
	Hb-Typing					
	PT	sec.				
	PTT	sec.				
	INR					
Biochemistry	Serum pH	-				
	HCO_3^-	mmol/l				
	Sodium	mmol/l				
	Potassium	mmol/l				
	Chloride	mmol/l				
	Calcium	mg%				
	Blood Glucose	mg%				
	BUN	mg%				
	Creatinine	mg%				
	Bilirubin total	mg%				
	direct Bilirubin	mg%				
	AST	U/l				
	ALT	U/l				
	Alk. Phosphatase	U/l				
	Total Protein	g%				
	Albumin	g%				
	Globulin	g%				
	Myoglobin					
	CPK	U/l				
	LDH	U/l				
Urine Analysis	Urine colour	-				
	Urine pH	-				
	Urine Albumin	0 - 4+				
	Urine protein	mg/dl				
	Urine specific gravity	g/l				
	Urine RBC	/HPF				
	Urine WBC	/HPF				

BIOGRAPHY

NAME	Mr. Andreas Ludwig Christian NEUMAYR
DATE OF BIRTH	11th June 1976
PLACE OF BIRTH	Regensburg, Germany
INSTITUTION ATTENDED	University of Regensburg, Germany 1997 - 2004 Degree obtained: M.D.
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	Kilimanjaro Christian Medical Center (KCMC), Moshi, Tanzania 2004 Position held: Intern
	Robert-Koch-Klinik, St. Georg Hospital, Leipzig, Germany 2004 - 2006 Position held: Assistenzarzt (Internal Medicine)
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