MAJOR ARTICLE

Age as a Risk Factor for Severe Manifestations and Fatal Outcome of Falciparum Malaria in European Patients: Observations from TropNetEurop and SIMPID Surveillance Data

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Previous studies have indicated that age is a risk factor for severe falciparum malaria in nonimmune patients. The objectives of this study were to reevaluate previous findings with a larger sample and to find out how strongly clinical outcomes for elderly patients differ from those for younger patients. Results of adjusted analyses indicated that the risks of death due to falciparum malaria, of experiencing cerebral or severe disease in general, and of hospitalization increased significantly with each decade of life. The case-fatality rate was almost 6 times greater among elderly patients than among younger patients, and cerebral complications occurred 3 times more often among elderly patients. Antimalarial chemoprophylaxis was significantly associated with a lower case-fatality rate and a lower frequency of cerebral complications. Women were more susceptible to cerebral complications than were men. Our study provides evidence that falciparum malaria is more serious in older patients and demonstrates that clinical surveillance networks are capable of providing quality data for investigation of rare events or diseases.

In regions of endemicity, severe *Plasmodium falciparum* malaria is seen primarily in children [1, 2] . However, several investigations involving nonimmune patients have indicated that severe [3–7] or fatal cases [3, 4, 7–11] are more common in older patients. Against that background, age-specific guidelines for treatment of falciparum malaria have become a matter of discussion.

Because severe malaria is a rare event in countries where it is not endemic, and because elderly patients constitute only a small fraction of nonimmune patients with malaria, data are sparse, which has hindered previous studies investigating the effect of age on disease severity from applying statistical methods of confounder control. Clinical surveillance networks for imported diseases, like the European TropNetEurop and its German sister network, Surveillance importierter Infektionen in Deutschland (SIMPID) [12], receive data on large numbers of malaria cases in nonimmune patients [13] from different age groups and, therefore, provide a unique opportunity for studies on rare disease events. The objectives of the present study were to reevaluate, with a larger sample size, the finding from previous, underpowered studies that age is a risk factor

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for severe falciparum malaria in nonimmune patients, and to find out how strongly elderly patients (age, ⩾60 years) differ from younger patients (age, 10–59 years) with respect to disease severity.

PATIENTS, MATERIALS, AND METHODS

The European network TropNetEurop and its German sister network, SIMPID, are designed to effectively detect emerging infections of potential regional, national, or global impact at their point of entry into the domestic population, to link clinical and epidemiological knowledge, and to serve as research platforms. Both networks are closely connected by common organizational and technical structures and identical reporting procedures. Surveillance reporting is performed by clinical member sites using a computerized reporting system. Electronic transmission of anonymous case information, comprising standardized demographic, epidemiological, and clinical data, to the central database assures rapid detection of sentinel events. Network membership is self-selected, and the network does not guarantee representative data collection for Europe. However, most major referral centers in Europe are represented (information is available at http://www.tropnet.net/ and http://www.simpid.de).

We conducted an observational study that involved patients with falciparum malaria reported to TropNetEurop and SIMPID during the period of January 1999 through July 2002. Data from both networks were pooled to increase statistical power. Included in the present analysis were data on Europeans returning to Europe with falciparum malaria. Excluded were data on cases involving immigrants, foreign visitors, expatriates, patients with mixed plasmodial or other concomitant infections, and children <10 years of age. Children and patients with concomitant infections were excluded to reduce baseline heterogeneity in the study population.

The influence of age on manifestations and outcome of severe disease was analyzed in crude and adjusted logistic regression models. Age was studied in an ordinal model, to investigate whether the risk for severe disease increases by decade of life, and in a dichotomous model, to compare elderly patients (age, ⩾60 years) with younger patients (age, 10–59 years). The investigated outcomes of severe disease were mortality, cerebral complications (as defined by World Health Organization criteria [1]), overall complications, and rate of hospitalization.

Risk factors for severe disease are likely to be unevenly distributed in an international survey population. Therefore, control for confounding variables may be an important issue in the estimation of unbiased age effects. The potential confounding variables considered in our analyses were sex, receipt of chemoprophylaxis, region where infection occurred, travel purpose, country where infection was notified, and time from onset of infection to receipt of treatment. Covariate selection for adjusted analyses was performed by backward elimination at a 5% α level. Multivariate analysis was done for each outcome to choose variables for adjusted analyses. All analyses were done with use of SAS software, release 8.01 (SAS Institute).

RESULTS

From January 1999 through July 2002, a total of 3028 patients with imported cases of falciparum malaria were reported to the TropNetEurop and SIMPID databases; 179 patients (5.9%) were ⩾60 years of age. A total of 1270 (41.9%) of the infections were imported by European nationals who were presently living and working in Europe; 78 (6.1%) of the affected patients were aged ⩾60 years. Further exclusion of patients with mixed infection, patients with multiple infections, and children aged <10 years resulted in a study population of 1181 patients.

Table 1 presents baseline characteristics of the study population. Patients were reported from 15 European countries, with Germany, the United Kingdom, Spain, and France contributing the bulk of patient data. Poland, Switzerland, Italy, Belgium, and Denmark contributed more-than-proportional numbers of elderly patients, compared with their overall case contribution. Nine of 10 patients were infected in Africa, mostly in the western region. Eastern and central Africa and the Madagascar region contributed more-than-proportional numbers of cases in elderly patients. Tourism, visits to relatives and friends, and business travel were the most frequent reasons for travel. Compared with younger patients, elderly patients traveled less often for tourist- or business-related reasons but more often for humanitarian reasons. Approximately two-thirds of the patients were male. Among elderly patients, the proportion of men was even higher. Receipt of pretravel advice and antimalarial chemoprophylaxis was more common among older patients. No differences were found with respect to travel duration and time from the onset of symptoms to presentation. Heterogeneity of the older and younger age groups could be confirmed at the 5% α level only for sex and prophylaxis. However, testing for heterogeneity of highly multidimensional characteristics, such as reporting country or region where infection occurred, may have failed to yield significant results as a result of limited statistical power.

The age range of patients in our study was 10–81 years. Age-specific frequencies of outcomes of severe disease are presented in table 2. Altogether, 113 cases (9.6%) of severe malaria were observed, consisting of 37 cases (3.1%) involving cerebral manifestations and 76 cases (6.4%) involving other severe or complicated manifestations. Seventeen patients with severe disease died, yielding a case-fatality rate of 1.4%. Eleven of the severe

Table 1. Baseline characteristics of patients in a study of falciparum malaria.

Characteristic	Patient group: Aged ⩾60 years (n = 78)	Patient group: Aged 10–59 years (n = 1103)	All (n = 1181)
Time to treatment, median days (IQR)[a]	4 (2–7)	4 (2–6)	4 (2–7)
Sex[b]			
No data	—	5 (0.5)	5 (0.4)
Male	62 (79.5)	700 (63.5)	762 (64.5)
Female	16 (20.5)	398 (36.1)	414 (35.1)
Received pretravel advice			
No data	31 (39.7)	526 (47.7)	557 (47.2)
Yes	28 (35.9)	285 (25.8)	313 (26.5)
No	19 (24.4)	292 (26.5)	311 (26.3)
Received prophylaxis[b]			
No data	7 (9.0)	76 (6.9)	83 (7.0)
Yes	38 (48.7)	416 (37.7)	454 (38.4)
No	33 (42.3)	611 (55.4)	644 (54.5)
Travel purpose			
No data	5 (6.4)	31 (2.8)	36 (3.0)
Tourism	43 (55.1)	666 (60.4)	709 (60.0)
Visiting friends and/or relatives	12 (15.4)	157 (14.2)	169 (14.3)
Business	9 (11.5)	157 (14.2)	166 (14.1)
Missionary/humanitarian	9 (11.5)	42 (3.8)	51 (4.3)
Other	0 (0)	50 (4.6)	50 (4.3)
Region where infection occurred			
No data	—	1 (0.1)	1 (9.7)
Africa			
Central	10 (12.8)	104 (9.4)	114 (9.7)
Eastern	23 (29.5)	169 (15.3)	192 (16.3)
Northern	—	3 (0.3)	3 (0.3)
Southern	2 (2.6)	97 (8.8)	99 (8.4)
Western	38 (48.7)	615 (55.8)	653 (55.3)
Other	5 (6.4)	114 (10.4)	119 (10.1)
Country where infection was reported			
Austria	2 (2.6)	41 (3.7)	43 (3.6)
Belgium	10 (12.8)	73 (6.6)	83 (7.0)
Czech Republic	1 (1.3)	27 (2.4)	28 (2.4)
Denmark	11 (14.1)	88 (8.0)	99 (8.4)
France	7 (9.0)	120 (10.9)	127 (10.8)
Germany	18 (23.1)	369 (33.5)	387 (32.8)
Ireland	—	5 (0.5)	5 (0.4)
Italy	4 (5.1)	22 (2.0)	26 (2.2)
Norway	—	5 (0.5)	5 (0.4)
Poland	2 (2.6)	7 (0.6)	9 (0.8)
Portugal	—	6 (0.5)	6 (0.5)
Spain	7 (9.0)	124 (11.2)	131 (11.1)
Sweden	—	19 (1.7)	19 (1.6)
Switzerland	5 (6.4)	18 (1.6)	23 (1.9)
United Kingdom	11 (14.1)	179 (16.2)	190 (16.1)

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range.

[a] Time from onset of symptoms.

[b] Significant group heterogeneity occurred at the 5% α level

Table 2. Age-specific frequency of outcomes of severe falciparum malaria.

Age group, years	No. of patients	Percentage of patients with			
		Fatal cases	Cerebral complications	Overall complications	Hospital admission[a]
10–19	50	0.0	0.0	4.0	70.0
20–29	290	0.7	1.0	6.2	79.0
30–39	369	0.5	1.9	7.3	79.7
40–49	225	2.2	6.2	13.8	81.8
50–59	169	2.4	4.7	14.2	85.2
60–69	56	3.6	5.4	8.9	73.2
70–79	20	10.0	10.0	30.0	95.0
80–89	2	0.0	0.0	0.0	100.0
Total	1181	1.4	3.1	9.6	80.3

[a] Values are missing for 39 patients.

cases and 4 of the fatal cases involved elderly patients (age, ⩾60 years). The overall hospitalization rate was 80.3%; however, information on care status was not available for 39 patients.

Table 3 summarizes the ORs and 95% CIs for the age-outcome associations derived from crude and adjusted logistic models. The effect of age on the frequency of certain outcomes was estimated twice for each outcome. First, we quantified the risk increase per additional decade of life, and, second, we quantified the risk for elderly patients compared with younger patients. As expressed by the adjusted OR, the risk of death due to falciparum malaria increased by ~85% per decade of life (OR, 1.85; 95% CI, 1.30–2.62). The case-fatality rate for older patients was ~6 times higher than that for younger patients (OR, 5.74; 95% CI, 1.78–18.47). The risk of developing cerebral complications increased by ~65% per decade of life (OR, 1.66; 95% CI, 1.31–2.12), and elderly patients had a 3-fold higher risk than did patients in the younger age group (OR, 3.29; 95% CI, 1.20–9.01). Prior receipt of antimalarial chemoprophylaxis was found to significantly reduce the risk of death due to disease (OR, 0.17; 95% CI, 0.04–0.74) or of development of cerebral complications (OR, 0.44; 95% CI, 0.20–0.96). Women had more than twice the risk of developing cerebral complications compared with men (OR, 2.63; 95% CI, 1.33–5.20).

The risk of developing severe disease in general was found to increase by ~30% per decade of life (OR, 1.32; 95% CI, 1.14–1.53). However, elderly patients were compared with younger patients by Student's *t* test, and only a nonsignificant result was attained (OR, 1.64; 95% CI, 0.81–3.30).

The frequency of hospital admission also was found to increase with each decade of life (OR, 1.21; 95% CI, 1.06–1.39), whereas dichotomous comparison again only indicated a nonsignificant elevated risk for elderly patients (OR, 1.30; 95% CI, 0.64–2.67). It should be noted that adjustment for notifying country evened out imbalances that resulted from country-specific admission preferences. For example, most patients who notified the networks from Ireland, Switzerland, and Belgium received outpatient treatment, whereas patients who notified the network from other countries were more often hospitalized. Women more often received inpatient treatment than did men (OR, 2.02; 95% CI, 1.36–2.99). Length of inpatient hospital stay was considered to be a possible indicator for disease severity, too. However, because it was an optional surveillance parameter, data were available for only 179 patients, 15 of whom were from the old age group and 164 of whom were from the younger age group. Analysis of this subset of patients indicated that 50% of the hospitalized patients aged ⩾60 years spent ⩾7 days (interquartile range, 4–10 days) in the hospital, whereas, for the younger age group, the median duration of inpatient stay was only 5 days (interquartile range, 4–7 days). However, because of the limited sample size used in the subanalysis, this finding may be a result of chance ($P = .1297$).

DISCUSSION

Several investigations have indicated that older age is a risk factor for severe [3–7] or fatal falciparum malaria [3, 4, 7–11] in nonimmune patients. However, because severe malaria is a rare finding when patients are treated in a timely manner, and because elderly patients account only for a minor fraction of

Table 3. Crude and adjusted effect of age on different outcomes of *Plasmodium falciparum* infection in European patients.

Outcome, age model	OR (95% CI)	
	Crude analysis	Adjusted analysis
Death		
Per decade	1.73 (1.25–2.38)	1.85 (1.30–2.62)[a]
Old vs. young	4.53 (1.44–14.24)	5.74 (1.78–18.47)[a]
Cerebral complications		
Per decade	1.53 (1.22–1.92)	1.66 (1.31–2.12)[b]
Old vs. young	2.29 (0.87–6.06)	3.29 (1.20–9.01)[b]
Overall complications		
Per decade	1.33 (1.16–1.52)	1.32 (1.14–1.53)[c]
Old vs. young	1.61 (0.83–3.15)	1.64 (0.81–3.30)[c]
Hospitalization		
Per decade	1.13 (1.00–1.27)	1.21 (1.06–1.39)[d]
Old vs. young	0.97 (0.53–1.81)	1.30 (0.64–2.63)[d]

NOTE. Old, age of ⩾60 years; young, age of 10–59 years.

[a] Adjusted for prior receipt of antimalarial chemoprophylaxis.
[b] Adjusted for prior receipt of antimalarial chemoprophylaxis and sex.
[c] Adjusted for notifying country.
[d] Adjusted for sex and notifying country.

nonimmune patients with malaria, previous analyses were considerably impaired by limited sample size. The objective of the present study was to reevaluate the findings from previous investigations in adjusted analyses that control for potential confounding variables and to determine how greatly the clinical course in elderly patients aged ⩾60 years differs from that in younger patients. Comparison of the number of severe cases included in the present study with data from former studies confirms that clinical surveillance networks like TropNetEurop and SIMPID are highly capable of providing superior data for studies on rare disease-associated events.

Data analyses yielded significant results, demonstrating that the risks of death due to falciparum malaria (OR, 1.85; 95% CI, 1.30–2.62), of experiencing cerebral (OR, 1.66; 95% CI, 1.31–2.12) or severe disease in general (OR, 1.32; 95% CI, 1.14–1.53), and of hospitalization (OR, 1.21; 95% CI, 1.06–1.39) increased with each decade of life. Prior receipt of antimalarial chemoprophylaxis was significantly associated with a lower case-fatality rate (OR, 0.17; 95% CI, 0.04–0.74) and with a lower frequency of cerebral complications (OR, 0.44; 95% CI, 0.20–0.96). Women were found to have a higher risk of developing cerebral complications (OR, 2.63; 95% CI, 1.33–5.20) than were men. However, it should be noted that we did not perform systematic risk factor analyses to study the effects of receipt of chemoprophylaxis and sex. We found that the case-fatality rate and the risk of developing severe disease in general increase with age, which is basically consistent with the findings from previous unadjusted or less-extensive analyses [3–11], although a quantitative comparison of the findings is impossible to perform because of methodological differences between analyses. To our knowledge, the effect of age on the occurrence of cerebral complications has not previously been analyzed separately in nonimmune patients, although cerebral malaria has been reported as a manifestation of severe disease in previous studies [4, 5, 7].

To date, elderly patients (age, ⩾60 years) have been compared with younger patients only in a recent Danish case-control study [6]. However, that study included only 2 cases of severe disease. Our comparison provides significant evidence that the risk of death due to falciparum malaria (OR, 5.74; 95% CI, 1.78–18.47) and of development of cerebral complications (OR, 3.29; 95% CI, 1.20–9.01) is several times higher among elderly, nonimmune patients. OR estimates from adjusted analyses also indicated that there were higher risks for severe disease in general and for hospitalization. However, the differences in risk were more subtle and could not be confirmed statistically, which may be explained by power limitations related to the high age cutoff applied in our study. Power limitations caused by missing values might have prevented statistical confirmation of prolonged duration of inpatient hospital stay observed in elderly patients.

The results of the present study confirm that the risks of death and development of severe complications due to falciparum malaria increase with age in nonimmune patients. But how can it be explained that, in nonimmune populations, severe malaria is more often seen in older patients, whereas, in semi-immune populations, severe malaria is a problem among younger persons? One explanation might be that our analysis could be confounded. However, because neither adjustment for receipt of chemoprophylaxis or treatment delay nor adjustment for other potential confounding variables reversed the direction of the detected age-outcome associations, we consider confounding an unlikely explanation. Another explanation might be that our findings only reflect higher background mortality and a more-fragile health state among persons in older age groups. However, data analyses in this investigation detected a continuous risk increase over the whole age spectrum, whereas the risk for severe disease was shown to decrease with age in a semi-immune population [2]. Thus, this explanation is most likely insufficient. A more convincing explanation might be that our findings reflect a decreasing capability of the aging immune system to mount defensive responses against previously unencountered infectious agents. This hypothesis is supported by findings of Gjørup and Rønn [6], who detected significantly higher rates of parasitemia in elderly, nonimmune patients. It would also be consistent with the observation that people in areas of endemicity who are regularly exposed to plasmodia are not at higher risk of developing complications when they get older. Another explanation, which centers on age-specific immune responses, was given by Baird et al. [3], who hypothesized that the balance between protective and harmful immune responses might shift towards the harmful side with increasing age. Again, to be consistent with the different risk situation in areas of endemicity, this shift would have to be more pronounced in previously unchallenged hosts. In general, elderly patients experience increased susceptibility to and morbidity associated with many infectious diseases, mostly due to comorbidity [14, 15]. Presumably, a decreased ability to mount an adequate immune response plays an important additional role. Results from various studies indicate a shift from Th1 to Th2 response with increasing age, among other responses, leading to decreased cellular response [16, 17]. The main mechanisms of early host response to plasmodial infection are not well elucidated.

It remains to be studied whether there is a connection between the immunological response to malaria and age-related changes in the immune system. To uncover the pathophysiological mechanisms behind the findings of this study will be an objective for future investigations. The finding that female sex was associated with a higher risk of cerebral complications might trigger further research, too.

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References

1. Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg **2000**; 94:S1–90.
2. Luxemburger C, Ricci F, Nosten F, Raimond D, Bathet S, White NJ. The epidemiology of severe malaria in an area of low transmission in Thailand. Trans R Soc Trop Med Hyg **1997**; 91:256–62.
3. Baird JK, Masbar S, Basri H, Tirtokusumo S, Subianto B, Hoffman SL. Age-dependent susceptibility to severe disease with primary exposure to *Plasmodium falciparum.* J Infect Dis **1998**; 178:592–5.
4. Calleri G, Lipani F, Macor A, Belloro S, Riva G, Caramello P. Severe and complicated falciparum malaria in Italian travelers. J Travel Med **1998**; 5:39–41.
5. Jensenius M, Ronning EJ, Blystad H, et al. Low frequency of complications in imported falciparum malaria: a review of 222 cases in southeastern Norway. Scand J Infect Dis **1999**; 31:73–8.
6. Gjorup IE, Ronn A. Malaria in elderly nonimmune travelers. J Travel Med **2002**; 9:91–3.
7. Schwartz E, Sadetzki S, Murad H, Raveh D. Age as a risk factor for severe *Plasmodium falciparum* malaria in nonimmune patients. Clin Infect Dis **2001**; 33:1774–7.
8. Buck RA, Eichenlaub D. Prognostische Faktoren der Malaria tropica—Ergebnisse einer Evaluationsstudie in der Bundesrepublik Deutschland 1963–1988. Gesundheitswesen **1994**; 56:29–32.
9. Schoneberg I, Strobel H, Apitzsch L. Erkrankungen an Malaria in Deutschland 1998/99—Ergebnisse einer Einzelfallerhebung des Robert-Koch-Institutes. Gesundheitswesen **2001**; 63:319–25.
10. Greenberg AE, Lobel HO. Mortality from *Plasmodium falciparum* malaria in travelers from the United States, 1959 to 1987. Ann Intern Med **1990**; 113:326–7.
11. Zastrow KD, Dieckmann S, Schoneberg I. Reisekrankheit Malaria—Einschleppung nach Deutschland 1988. Gesundheitswesen **1993**; 55:136–9.
12. Anonymous. Reiseassoziierte Infektionskrankheiten in Deutschland 2001. Epidemiologisches Bulletin **2002**:285–96.
13. Jelinek T, Schulte C, Behrens R, et al. Imported falciparum malaria in Europe: sentinel surveillance data from the European network on surveillance of imported infectious diseases. Clin Infect Dis **2002**; 34: 572–6.
14. Castle SC. Clinical relevance of age-related immune dysfunction. Clin Infect Dis **2000**; 31:578–85.
15. Yoshikawa TT. Epidemiology and unique aspects of aging and infectious diseases. Clin Infect Dis **2000**; 30:931–3.
16. Sandmand M, Bruungsgaard H, Kemp K, Andersen-Ranberg K, Pedersen AN, Skinhøj P. Is ageing associated with a shift in the balance between type 1 and type 2 cytokines in humans? Clin Exp Immunol **2002**; 127:107–14.
17. Khann KV, Markham RB. A perspective on cellular immunity in the elderly. Clin Infect Dis **1999**; 28:710–3.