Elevated Values of C-Reactive Protein Induced by Imported Infectious Diseases: A Controlled Cross-Sectional Study of 11,079 Diseased German Travelers Returning from the Tropics and Subtropics

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Abstract. The present controlled cross-sectional study aimed to assess elevated values of C-reactive protein (CRP), a positive acute-phase protein, induced by imported infectious diseases (IDs) seen in patients consulting the University of Munich (1999–2015) after being in the tropics/subtropics. The analysis investigated data sets from 11,079 diseased German travelers (cases) returning from Latin America (1,986), Africa (3,387), and Asia (5,706), and from 714 healthy Germans who had not recently traveled (controls). The proportions of elevated values of CRP (> 0.5 mg/dL) were significantly larger among cases (44.3%) than among controls (20.7%). Among cases, this proportion was largest among males (49.2%) in comparison to females (39.9%), among travelers with short travel duration of 1–14 days (49.6%) in comparison to travelers with a travel duration of > 180 days (30.8%), and with travel destination in Africa (47.0%) in comparison to Asia (44.2%) and Latin America (39.9%), among all-inclusive travelers (47.4%) in comparison to business travelers (46.7%) and backpackers (44.1%), and among patients presenting with fever (70.9%) and arthralgia (54.3%). The study identified various imported IDs with significantly larger proportions of elevated values of CRP including viral (cytomegalovirus infection [94.7%], influenza [88.9%], infectious mononucleosis [71.8%]), bacterial (typhoid fever [100%], paratyphoid fever [92.9%], shigellosis [76.8%], rickettsiosis [74.2%], *Salmonella* enteritis [71.3%], *Campylobacter* infection [68.7%]), and protozoan (vivax malaria [100%], ovale malaria [100%], falciparum malaria [95.4%], noninvasive *Entamoeba* infection [65.9%]) IDs. This study demonstrates that elevated values of CRP can be a useful laboratory finding for travelers returning from the tropics/subtropics, as these findings are typically caused mainly by certain imported bacterial IDs, but also by viral and protozoan IDs.

INTRODUCTION

Since its discovery in 1930, the human C-reactive protein (CRP) has been recognized as a classical positive acute-phase protein.^{1,2} Any acute or chronic inflammation in the body leads to a release of several cytokines from macrophages and adipocytes.³ CRP is a sensitive inflammatory biomarker, as its serum concentration correlates with the extent of any cell damage. Cell damage can be caused by any injuries, neoplasms, immunologic disorders, or infections, consequently, elevated values of CRP are not specific to any particular disorder.⁴ Mainly interleukin-6, interleukin-1, and leukemia inhibitory factor cause rapid and accelerated synthesis of CRP in the liver.⁵ As elevated values of CRP can be measured even in a few hours after cell damage and as its serum half time is only approximately 18 hours, serum CRP determinations are widely performed in clinical practice to detect and monitor many acute inflammatory human diseases.⁶ The normal range of CRP is generally defined as values up to 0.5 milligrams per deciliter (mg/dL), regardless of sex and age of the patients. However, several studies have shown that males and elderly individuals had significantly higher normal levels of CRP than females and younger individuals.⁷ Initially considered only as an acute-phase protein, CRP is recently being used as a distinct and sensitive biomarker in terms of predicting the risk of cardiovascular diseases and cancer.^{8,9}

Elevated values of CRP are often seen in patients with infectious diseases (IDs), mainly in those with acute bacterial IDs. In contrast to this, patients with acute viral infections tend to have normal or slightly increased CRP concentrations.^{10,11} For two protozoan diseases, specific cell binding of CRP was described. Studies in Tanzania,¹² Gambia,¹³ and India¹⁴ have found that CRP level was highly correlated with parasite density, severity, and morbidity among patients with malaria. They have shown direct evidence for an important phagocytic functional interaction of CRP by triggering the complement pathway after a 2.3-fold increased binding with *Plasmodium*-infected erythrocytes, which caused enhanced hemolysis.¹⁵ CRP binds cells via the characteristic ligands phosphocholine and phosphoethanolamine, which are also expressed on the surface of dying or dead cells, to initiate phagocytosis.¹⁶ For *Leishmania donovani*, it was shown that CRP binds to another ligand, the lipophosphoglycan component of the promastigote cell surface, which leads to an increased uptake of this obligate intracellular parasite into human monocyte-derived macrophages.¹⁷

As many IDs are endemic to tropical and subtropical regions, travelers going to such destinations are particularly at risk of acquiring these IDs.¹⁸ Data on this subject are rare and no systematic study on infection-induced elevated values of CRP among travelers has been reported to date, despite the immense increase in international mobility. The number of international travels worldwide has increased from 25 million in 1950, to 625 million in 1999, and to 1,184 million in 2015. In addition to the traditional favorite destinations of Europe and North America, many new destinations have emerged, especially in tropical and subtropical countries. In 2015, the average annual growth in international travels worldwide was 4.4%, with above-average growth in the

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Caribbean (7.4%), in Central America (7.1%), and in Southeast Asia (5.1%).¹⁹ In 2015, about 21.7 million individuals traveled from Germany to destinations outside of Europe. Of them, 2.1 million traveled to Latin America, 3.4 million to Africa, and 9.0 million to Asia.²⁰

The aim of the present controlled cross-sectional study was to assess the validity of the laboratory findings for elevated or immensely elevated values of CRP induced by imported IDs. The study was performed using data from a large number of patients who consulted the Division of Infectious Diseases and Tropical Medicine (DITM) at the Medical Center of the University of Munich, between January 1999 and December 2015, after being in the tropics and subtropics. Diverse findings from the data of these consultations showing the spectrum of imported IDs and the results on the validity of unspecific hematological and serological parameters were already published.^{18,21–29} These 11,079 diseased returned travelers (cases) were diagnosed and treated at a single study site, with an additional sample of 714 healthy individuals of German origin who had not recently traveled to the tropics or subtropics (controls). Consequently, all cases and controls were subject to the same standardized process, allowing for maximal comparability of the data.

MATERIALS AND METHODS

Database. The DITM has been collecting data on sociodemographics (sex, age, and origin), travel (duration, destination, and type of travel), clinical history and symptoms, diagnostics, and—if applicable—diagnosis data of individuals consulting its outpatient travel clinic for treatment or medical checkup. From January 1999 to December 2015, the DITM registered 41,899 individuals with complete data sets. Of them, 24,645 (58.82%) individuals had symptoms after traveling to the tropics and subtropics (Latin America, Africa, or Asia), 8,610 (20.55%) individuals did not have symptoms and had not recently traveled to the tropics and subtropics, 5,303 (12.66%) individuals had symptoms but had not recently traveled to the tropics and subtropics, and 3,341 (7.97%) individuals did not have symptoms after traveling to the tropics and subtropics. Among patients who consulted at DITM several times because of a certain disease, the symptoms presented here are those from their first visit.

Study population: cases and controls. Of the 24,645 patients returning from traveling in the tropics and subtropics, 21,361 (86.67%) were of German origin (defined as born in Germany). Among them, 11,079 (51.87%) patients had full data sets available on CRP, and were thereby defined as cases. The cases were grouped by type of travels as follows: 1,327 (11.98%) were business travelers (defined as those who were primarily on travel because of business or related issues), 2,181 (19.69%) were all-inclusive travelers (defined as those who did not organize travel by themselves, including package holidays), and 6,070 (54.79%) were backpackers (including low-budget and adventure travelers). The remaining 1,501 (13.55%) patients comprised a miscellaneous group of students, scientists, missionaries, volunteers, and other persons with travel activities, which could not be clearly defined.

Of the 8,610 healthy individuals who consulted the DITM for medical checkup before travel and had not recently traveled to the tropics and subtropics, 7,484 (86.92%) were of German origin. Among these healthy individuals, 714 (9.54%)

had full data sets available on CRP, and were thereby defined as controls.

All findings of this study are presented separately for females and males, as sex was unequally distributed among cases and controls. The proportion of females was significantly ($P < 0.01$) higher among cases (52.51%) than among controls (41.74%).

Study design. In this study, all patients consulted the DITM, at which time the independent variables (exposure as sociodemographics and travel) and dependent variables (outcomes as symptoms, diagnostics, and diagnosis) were assessed simultaneously: transversal study or cross-sectional study. The dependent variables were not influenced by the study design: noninterventional or observational study. The descriptive part of the study compared the prevalence of elevated or immensely elevated values of CRP among cases with certain IDs and among controls: prevalence study. The analytical part of the study compared these prevalences among cases with certain IDs and further with those of the controls: controlled study.

Laboratory analysis. Blood samples were taken from all individuals at first visit to the DITM before any therapeutic drug administration. Samples were collected in S-Monovette[®], serum gel with clotting activator-coated tubes (Sarstedt, Nümbrecht, Germany). Generally, the serum was stored not longer than 8 hours, and remained under permanent cooling at 2 to 8°C, and without freezing. The serum concentration of CRP was analyzed exclusively on the same day of taking blood by applying turbidimetry with AU5832 (Beckman Coulter, Brea, CA). The reference range of this serological parameter was defined according to in-house standards of the DITM.³⁰ The reference range of CRP is defined as serum concentration up to 0.5 mg/dL, regardless of sex and age of the patients. In the present study, values of CRP above the cutoff level of the reference range were defined as “elevated values”; and values of CRP above 5.0 mg/dL (10-fold higher than cutoff level) were defined as “immensely elevated values.”

Infectious diseases. The study detected 41 imported IDs, in which more than four cases were reported: 11 viral, seven bacterial, 13 protozoan, seven helminthic, and three ectoparasitic IDs. These 41 IDs comprised 2,525 laboratory confirmed cases with complete data sets. Only IDs with exact laboratory confirmation were considered in this study. Clinically suspected or probable cases were not included (Supplemental Table 1).

Data analysis. The database of the DITM was the source of all data analyzed in the present study. The descriptive analysis was performed by Excel Worksheet (Microsoft, Redmond, WA). The proportions of elevated values of CRP with 95% confidence intervals were used to assess significant differences between cases and controls, between females and males, and between different age groups. Furthermore, among cases, to assess significant differences between females and males, between different travel durations, travel destinations, and types of travel, between the principal symptoms, and between cases with certain imported IDs. Bivariate approximative tests (χ^2 tests) were conducted using EpiInfo, version 7 (Centers for Disease Control and Prevention, Atlanta, GA) and Stata software, version 9.0. (Stata Corporation, College Station, TX). Significant differences were defined as P values below 0.05.

TABLE 1

Elevated and immensely elevated values of C-reactive protein (CRP) induced by imported infectious diseases among 11,079 diseased German travelers returning from the tropics and subtropics (cases)

Interpretation of value	Females			Males			Total		
	Value of CRP			> 0.5 mg/dL			> 0.5 mg/dL		
	Total	Elevated	Immensely elevated	Total	Elevated	Immensely elevated	Total	Elevated	Immensely elevated
Cases (%)	5,818 (100)	2,319 (39.86)	654 (11.24)	5,261 (100)	2,589 (49.21)	786 (14.94)	11,079 (100)	4,908 (44.30)	1,440 (13.00)
95% CI		(38.60–41.12)	(10.43–12.05)		(47.86–50.56)	(13.98–15.90)		(43.38–45.23)	(12.37–13.62)
Controls (%)	298 (100)	58 (19.46)	8 (2.68)	416 (100)	90 (21.63)	12 (2.88)	714 (100)	148 (20.73)	20 (2.80)
95% CI		(14.97–23.96)	(0.85–4.52)		(17.68–25.59)	(1.28–4.49)		(17.75–23.70)	(1.59–4.01)
Total of 41 IDs (%)	1,260 (100)	553 (43.89)	151 (11.98)	1,265 (100)	676 (53.44)	213 (16.84)	2,525 (100)	1,229 (48.67)	364 (14.42)
95% CI		(41.15–46.63)	(10.19–13.78)		(50.69–56.19)	(14.78–18.90)		(46.72–50.62)	(13.05–15.79)
Number of IDs with significantly larger proportions	NA	10	5	NA	13	7	NA	13	8
IDs with significantly larger proportions of elevated or immensely elevated values of CRP compared to those of all cases (%)	NA			NA			NA		
	NA	Vivax malaria (100)	Vivax malaria (57.14)	NA	Vivax malaria (100)	Vivax malaria (71.43)	NA	Vivax malaria (100)	Vivax malaria (64.29)
	NA	Typhoid fever (100)	Typhoid fever (75.00)	NA	Typhoid fever (100)	Typhoid fever (66.67)	NA	Typhoid fever (100)	Typhoid fever (69.23)
	NA	0	0	NA	Ovale malaria (100)	Ovale malaria (80.00)	NA	Ovale malaria (100)	Ovale malaria (66.67)
	NA	Falciparum malaria (88.24)	Falciparum malaria (52.94)	NA	Falciparum malaria (100)	Falciparum malaria (50.00)	NA	Falciparum malaria (95.35)	Falciparum malaria (51.16)
	NA	CMV infection (100)	0	NA	CMV infection (90.91)	0	NA	CMV infection (94.74)	0
	NA	Paratyphoid fever (100)	0	NA	Paratyphoid fever (87.50)	0	NA	Paratyphoid fever (92.86)	0
	NA	0	0	NA	Influenza (85.71)	0	NA	Influenza (88.89)	0
	NA	Shigellosis (75.41)	Shigellosis (27.87)	NA	Shigellosis (78.43)	0	NA	Shigellosis (76.79)	Shigellosis (25.89)
	NA	Rickettsiosis (69.23)	0	NA	Rickettsiosis (77.50)	0	NA	Rickettsiosis (74.24)	0
	NA	Infectious mononucleosis (72.22)	0	NA	Infectious mononucleosis (71.43)	0	NA	Infectious mononucleosis (71.79)	0
	NA	Salmonella enteritis (62.32)	0	NA	Salmonella enteritis (79.73)	Salmonella enteritis (31.08)	NA	Salmonella enteritis (71.33)	Salmonella enteritis (25.87)
	NA	Campylobacter infection (64.86)	Campylobacter infection (25.41)	NA	Campylobacter infection (71.67)	Campylobacter infection (33.05)	NA	Campylobacter infection (68.66)	Campylobacter infection (29.67)
	NA	0	0	NA	Non-invasive Entamoeba inf. (67.86)	0	NA	Non-invasive Entamoeba inf. (65.91)	0
	NA	0	0	NA	0	Invasive Entamoeba inf. (75.00)	NA	0	Invasive Entamoeba inf. (60.00)

CI = confidence interval; CMV = human cytomegalovirus; inf = infection; NA = not applicable. In the present controlled cross-sectional study, 714 healthy Germans without having recently traveled to the tropics and subtropics served as controls.

Ethical considerations. Ethical clearance for the study protocol was provided by the Ethical Committee of the Medical Faculty at the University of Munich, Germany. Clinical and laboratory data were only used from patients who provided written informed consent, or in the case of minors, had general written informed consent from the legal caretakers.

RESULTS

Demographic data of cases and controls. Data from 11,079 cases and 714 controls fulfilled the inclusion criteria. Among the cases, 52.51% (5,818) were female, with this proportion being significantly ($P < 0.01$) higher than among the controls (41.74% [298]). Of the cases, the age range was 10 months to 92 years, with a median of 34.5 years, and an interquartile range (IQR) of 26.8–48.3 years. Of the controls, the age range was 11 months to 92 years, with a median age of 39.8 years, and an IQR of 28.3–52.8 years. Grouped into age groups of 0–19 years, 20–64 years, and 65–92 years, the corresponding proportions among the cases were 5.92% (656), 87.70% (9,716), and 6.38% (707), respectively; and among controls: 12.75% (91), 77.59% (554), and 9.66% (69), respectively (Table 1 and Supplemental Table 1).

Values of CRP among cases. The proportions of elevated and immensely elevated values of CRP among male cases (49.21% and 14.94%, respectively) were significantly higher than among female cases (39.86% and 11.24%, respectively) in age groups 20–64 years and 65–92 years, but not in age group 0–19 years. The proportion of elevated values of CRP among cases in the three different age groups 0–19 years (40.40%), 20–64 years (44.70%), and 65–92 years (42.43%) were not significantly different (Supplemental Table 1).

Values of CRP among controls. The proportions of elevated and immensely elevated values of CRP among male controls (21.63% and 2.88%, respectively) were comparable with those among female controls (19.46% and 2.68%, respectively), and also in all three age groups. The proportion of elevated values of CRP among controls in age group 0–19 years (6.59%) was significantly lower than in the age groups 20–64 years (22.92%) and 65–92 years (21.43%) (Supplemental Table 1).

Values of CRP compared between cases and controls. The proportions of elevated and immensely elevated values of CRP were significantly higher among cases (44.30% and 13.00%, respectively) than among controls (20.73% and 2.80%, respectively). The proportion of elevated values of CRP among female cases (39.86%) was significantly higher than among controls (19.46%) in age group 0–19 years and 20–64 years, but not in age group 65–92 years. The proportion of elevated values of CRP among male cases (49.21%) was significantly higher than among controls (21.63%), and also in each of the three age groups (Supplemental Table 1).

Values of CRP and travel data. Among the 11,079 diseased German travelers returning from the tropics and subtropics, the range of travel duration was 1 day to 50 years, with a median of 21 days, and an IQR of 14–35 days. The proportion of elevated values of CRP was significantly higher among cases with short travel durations of 1–14 days (49.56%) and 15–30 days (45.77%) in comparison to cases with travel duration of 31–60 days (40.69%), of 61–180 days (32.66%), and of > 180 days (30.80%).

The proportion of elevated values of CRP was significantly higher among cases with a travel destination in Africa (47.00%) than in Latin America (39.93%), whereas in Asia it was in between (44.22%). The proportion of elevated values of CRP was highest among all-inclusive travelers (47.36%), followed by business travelers (46.65%) and backpackers (44.05%) (Supplemental Table 1).

Values of CRP and symptoms. In the database, 15 different symptoms were registered systematically. The most documented symptoms were diarrhea (40.16%), fever (34.19%), nausea (18.82%), skin disorders (17.09%), and arthralgia (15.00%). The proportion of elevated values of CRP was significantly higher among cases with fever (70.86%) and arthralgia (54.33%) than among those with nausea (44.80%), diarrhea (42.84%), and skin disorder (38.72%) (Supplemental Table 1).

Frequently imported IDs. In the study population, 41 IDs had at least five laboratory confirmed cases with known values of CRP. Fifteen IDs had more than 19 cases each, and among them six were intestinal infections with: *Blastocystis* (618 cases), *Giardia* (390), *Campylobacter* (418), *Shigella* (112), *Salmonella* (143), and *Entamoeba* (44) spp. The remaining nine frequently documented IDs were dengue fever (259), rickettsiosis (66), cutaneous larva migrans (49), cryptosporidiosis (44), falciparum malaria (43), infectious mononucleosis (39), cyclosporiasis (30), schistosomiasis (28), and chikungunya (20) (Supplemental Table 1).

IDs with largest proportions of elevated values of CRP. Compared with the mean proportion of all 11,079 cases, the present study identified 13 IDs with significantly larger proportions of elevated values of CRP, namely: vivax malaria (100%), typhoid fever (100%), ovale malaria (100%), falciparum malaria (95.35%), human cytomegalovirus (CMV) infection (94.74%), paratyphoid fever (92.86%), influenza (88.89%), shigellosis (76.79%), rickettsiosis (74.24%), infectious mononucleosis (71.79%), *Salmonella* enteritis (71.33%), *Campylobacter* infection (68.66%), and noninvasive *Entamoeba* infection (65.91%).

Compared with the mean proportion of all 5,261 male cases, the present study identified three IDs with significantly larger proportions of elevated values of CRP: ovale malaria (100%), influenza (88.89%), and noninvasive *Entamoeba* infection (65.91%). The proportions were not significantly elevated among the corresponding female cases.

None of the proportions of CRP values for any helminthic IDs (cutaneous larva migrans, schistosomiasis, hookworm [*Necator* and *Ancylostoma* spp.] infection, trichuriasis, ascariasis, and oxyuriasis), or for any ectoparasitic IDs (scabies, myiasis, and tungiasis) considered in this study were significantly elevated compared with the mean proportions of all 11,079 cases (Supplemental Table 1).

IDs with largest proportions of immensely elevated values of CRP. Compared with the mean proportion of all 11,079 cases, the present study identified eight IDs with significantly larger proportions of immensely elevated values of CRP: vivax malaria (64.29%), typhoid fever (69.23%), ovale malaria (66.67%), falciparum malaria (51.16%), shigellosis (25.89%), *Salmonella* enteritis (25.87%), *Campylobacter* infection (29.67%), and invasive *Entamoeba* infection (60.00%).

Compared with the mean proportion of all 5,261 male cases, the present study identified three IDs with significantly larger proportions of immensely elevated values of CRP, whose proportions were not significantly elevated among

the corresponding female cases: ovale malaria (80.00%), *Salmonella* enteritis (31.08%), and invasive *Entamoeba* infection (75.00%). Although in all 5,818 female cases, the present study identified one ID with significantly larger proportions of immensely elevated values of CRP, whose proportion was not significantly elevated among the corresponding male cases: shigellosis (27.87%).

None of the proportions of immensely elevated values of CRP for any viral (dengue fever, infectious mononucleosis, chikungunya, CMV infection, herpes simplex, herpes zoster, influenza, chronic hepatitis C, asymptomatic human immunodeficiency virus [HIV] infection, acute HIV infection, and hepatitis A), helminthic, or ectoparasitic IDs considered in this study were significantly elevated compared with the mean proportions of all 11,079 cases (Supplemental Table 1).

DISCUSSION

The present study is the largest controlled cross-sectional study assessing the validity of the laboratory findings of elevated values of CRP induced by imported IDs. The study was performed with data from 11,079 patients who consulted the DITM at the Medical Center of the University of Munich between 1999 and 2015, after being in the tropics and subtropics.

Overall, this study showed larger proportions of elevated values of CRP among cases compared with controls. This finding was expected, as several of the identified imported IDs cause significantly larger proportions of elevated values of CRP. All findings of the present study were separately demonstrated for females and males, as sex was unequally distributed among cases and controls. The proportion of females was significantly higher among cases than among controls.

Furthermore, the proportions of elevated and immensely elevated values of this inflammatory parameter among male cases were significantly larger than among female cases. This was partially caused by the fact that, in clinical practice, the reference range of CRP is generally defined as serum concentration up to 0.5 mg/dL, regardless of patients' sex and age. However, several studies have shown sex and age-related differences concerning the values of CRP.⁷ It is assumed that males and elderly individuals have significantly higher normal levels of CRP than females and younger individuals. These findings were also seen in the present study. Among cases, males had significantly larger proportions of elevated or immensely elevated values of CRP than females. Among controls, males had only slightly larger proportions than females, and this difference was not significant. For both sexes, the proportions of elevated and immensely elevated values of CRP were higher in adults compared with those in children and adolescents, whereas these differences were much higher in controls than in cases.

In the present study, the difference concerning the proportion of elevated and immensely elevated values of CRP among male cases compared with that among female cases was higher than seen in the controls. This association between elevated values of CRP and sex was highly confounded by several IDs. The overall proportion of female cases in the present study was 52.51%, with this group accounting for a larger proportion among those with cryptosporidiosis (68.18%), myiasis (66.67%), herpes simplex (60.00%), trichuriasis (60.00%), tungiasis (60.00%), *Streptococcus* pharyngitis (60.00%), scabies (57.14%), cyclosporiasis (56.67%), hookworm infection

(55.56%), and *Blastocystis hominis* infection (55.02%). None of these 10 IDs was identified to cause elevated values of CRP. In contrast to this, the overall proportion of male cases in the present study was 47.49%, with this group accounting for a larger proportion among those with ovale malaria (83.33%), invasive *Entamoeba* infection (80.00%), influenza (77.78%), typhoid fever (69.23%), noninvasive *Entamoeba* infection (63.64%), rickettsiosis (60.61%), falciparum malaria (60.47%), CMV infection (57.89%), paratyphoid fever (57.14%), and *Campylobacter* infection (55.74%). All 10 of these IDs were identified to cause elevated or immensely elevated values of CRP.

Furthermore, in the present study, the difference concerning the proportion of elevated and immensely elevated values of CRP among adult cases compared with those among young cases (0–19 years) was smaller than seen in the controls. This association between elevated values of CRP and age was confounded by several IDs. The overall proportion of young cases in the present study was 5.92%, with this group accounting for a larger proportion among those with paratyphoid fever (35.71%), infectious mononucleosis (23.08%), invasive *Entamoeba* infection (20.00%), ovale malaria (16.67%), *Salmonella* enteritis (11.89%), falciparum malaria (11.63%), typhoid fever (7.69%), and vivax malaria (7.14%). All these eight IDs were identified to cause elevated or immensely elevated values of CRP.

The present study found a strong correlation between CRP level and duration of travel: the longer the travel lasted, the larger were the proportions of elevated or immensely elevated values of CRP. This finding was expected, as this classical positive acute-phase protein is a very sensitive biomarker for acute IDs, which are more frequently seen among short-term travelers. The overall proportion of patients with travel duration of 1–14 days in the present study was 33.73%, with this group accounting for a larger proportion among those with influenza (77.78%), *Salmonella* enteritis (52.50%), vivax malaria (50.00%), ovale malaria (50.00%), infectious mononucleosis (47.37%), CMV infection (46.67%), shigellosis (46.24%), and *Campylobacter* infection (42.65%). All these eight IDs were identified to cause elevated or immensely elevated values of CRP.

In the present study, the proportion of elevated values of CRP was largest among travelers with travel destinations in Africa, followed by those in Asia and in Latin America. The overall proportion of travelers with travel destination in Africa was 30.57%, with this group accounting for a larger proportion among those with rickettsiosis (93.94%), falciparum malaria (90.70%), ovale malaria (66.67%), and vivax malaria (50.00%). All these four IDs were identified to cause elevated or immensely elevated values of CRP. In contrast to this, the overall proportion of travelers with travel destination in Latin America was 17.93%, whereas it was larger among those with mucocutaneous leishmaniasis (100%), tungiasis (60.00%), chikungunya (50.00%), myiasis (50.00%), and hookworm infection (33.33%). None of these five IDs was identified to cause elevated values of CRP. The overall proportion of travelers with travel destination in Asia was 51.50%, with this group accounting for a larger proportion among those with influenza (88.89%), cyclosporiasis (86.67%), acute HIV infection (80.00%), invasive *Entamoeba* infection (80.00%), typhoid fever (76.92%), dengue fever (74.52%), paratyphoid fever (71.43%), and

giardiasis (66.92%). Of these eight IDs, four IDs (influenza, invasive *Entamoeba* infection, typhoid fever, and paratyphoid fever) were identified to cause elevated or immensely elevated values of CRP, whereas the other four IDs were not. Consequently, the proportion of elevated values of CRP among travelers with travel destinations in Asia was in between those with travel destination in Africa or in Latin America.

In the present study, the proportion of elevated values of CRP was largest among all-inclusive travelers and business travelers, and lowest among backpackers. The overall proportion of backpackers was 54.79%, with this group accounting for a larger proportion among those with ascariasis (100%), acute HIV infection (100%), strongyloidiasis (80.00%), tungiasis (80.00%), paratyphoid fever (78.57%), typhoid fever (69.23%), cryptosporidiosis (72.73%), chronic hepatitis C (71.43%), and giardiasis (68.97%). Except paratyphoid fever and typhoid fever, none of the other seven IDs were identified to cause elevated values of CRP. In contrast to this, the overall proportion of all-inclusive travelers was 19.69% and of business travelers 11.98%, while it was larger among all-inclusive travelers with CMV infection (31.58%), rickettsiosis (22.73%), and influenza (22.22%); and among business travelers with invasive *Entamoeba* infection (40.00%), falciparum malaria (27.91%), influenza (22.22%), vivax malaria (21.43%), infectious mononucleosis (20.51%), and noninvasive *Entamoeba* infection (20.45%). All these nine IDs were identified to cause elevated or immensely elevated values of CRP.

In the present study, the proportion of elevated values of CRP was largest among travelers consulting the DITM with symptoms of fever, followed by among those with arthralgia, diarrhea, nausea, and skin disorder. The overall proportion of travelers with fever was 34.19%, with this group accounting for a larger proportion among those with vivax malaria (100%), ovale malaria (100%), paratyphoid fever (92.86%), falciparum malaria (90.70%), influenza (88.89%), typhoid fever (84.62%), infectious mononucleosis (84.62%), and CMV infection (78.95%). All these eight IDs were identified to cause elevated or immensely elevated values of CRP. One exception to note is that dengue fever (81.08%) was the only typical febrile imported ID, which was not found to cause elevated values of CRP.

The present study has some limitations. It has a cross-sectional design, and as such, all data on independent variables (e.g., travel) and dependent variables (e.g., ID) were collected at the same day of consultation. Consequently, only limited data on the clinical status before travel were available through patient interviews. In addition, no follow-up data, such as duration of IDs, which developed after consultation, could be collected. Furthermore, the data analysis assessed associations between independent and dependent variables, but their causal interpretation was limited. Finally, no absolute data on the number of travelers were available, so no exact calculations on relative risk could be provided by this study.

However, in contrast to other studies with large numbers of patients which were multicentric, this study provides a uniformity in patient referral patterns, consistency in coding of diagnoses by clinicians, and central laboratory reference facilities. As all patients were subject to the same standardized process, maximal comparability of the data was possible. In addition, the study population was restricted to travelers of German origin, as values of CRP may vary immensely between international populations, especially those living in

endemic regions for certain IDs.¹⁸ Consequently, the conclusions taken from this study are restricted to German travelers only. Finally, the great majority of cases presented here were diagnosed during routine work at the outpatient travel clinic of the DITM, so extensive laboratory tests were not performed when not clinically relevant. For example, biomolecular testing of norovirus, rotavirus, or *Escherichia* spp. among patients with diarrhea were not routinely performed, as an exact diagnosis had no consequence for treatment.

CONCLUSIONS

The present study has shown that there is high validity for the laboratory findings of values of CRP induced by imported IDs among travelers returning from the tropics and subtropics. This inflammatory parameter was significantly associated with several variables concerning demographics (sex, age), travel (duration, destination, and type of travel), and symptoms of patients. However, these associations were highly confounded by various IDs imported by diseased German travelers from the tropics and subtropics.

Fourteen IDs were identified with significantly larger proportions of elevated values of CRP compared with those of all cases: three viral (CMV infection, influenza, and infectious mononucleosis), six bacterial (typhoid fever, paratyphoid fever, shigellosis, rickettsiosis, *Salmonella* enteritis, and *Campylobacter* infection), and five protozoan (vivax malaria, ovale malaria, falciparum malaria, noninvasive *Entamoeba* infection, invasive *Entamoeba* infection) IDs. For helminthic and ectoparasitic IDs assessed in the present study, no single significant association with elevated values of CRP was identified. This study demonstrates that elevated values of CRP are useful laboratory findings for travelers returning from the tropics and subtropics, as they are typically caused by certain imported viral, bacterial, and protozoan IDs.

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