

Elevated Values of Clinically Relevant Transferases Induced by Imported Infectious Diseases: A Controlled Cross-Sectional Study of 14,559 Diseased German Travelers Returning from the Tropics and Subtropics

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Abstract. The aim of this controlled cross-sectional study was to assess the clinical validity of elevated values of three clinically relevant transferase enzymes (aspartate transaminase [AST], alanine transaminase [ALT], and gamma-glutamyl transferase [GGT]) induced by imported infectious diseases (IDs) seen among patients consulting the Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (from 1999 to 2014), after being in the sub-/tropics. Data sets of 14,559 diseased German travelers returning from Latin America (2,715), Africa (4,574), or Asia (7,270) and of 1,536 healthy controls of German origin without recent travels were analyzed. Among the cases, the proportions of those with elevated values of AST (7.8%) and of ALT (13.4%) were significantly larger than among controls (4.0% and 10.6%, respectively), whereas for GGT, no significant difference was found (cases: 10.0%; controls: 11.4%). The study identified IDs with significantly larger proportions of both AST and ALT (hepatitis A [100%/100%], cytomegalovirus [CMV] infection [77%/81%], chronic hepatitis C [67%/67%], infectious mononucleosis [65%/77%], typhoid fever [50%/50%], cyclosporiasis [45%/66%], dengue fever [43%/35%], malaria [20%/27%], and rickettsiosis [20%/24%]), of AST alone (paratyphoid fever [42%]), of ALT alone (giardiasis [20%]), and of GGT (hepatitis A [100%], infectious mononucleosis [71%], CMV infection [58%], rickettsiosis [20%], and dengue fever [19%]). The study demonstrates that the determination of AST and ALT among travelers returning from the sub-/tropics has a high clinical validity, as their elevated values are typically caused by several imported viral, bacterial, and protozoan IDs, whereas no additional clinical validity was found by the determination of GGT.

INTRODUCTION

In every living cell of all organisms, hundreds of enzymes determine the cells' metabolic pathways.¹ More than 77,000 enzymes are known and listed in the BRENDA enzyme information system.² Beside a few catalytic ribonucleic acid enzymes, enzymes are proteins, catalyzing more than 5,000 described biochemical reactions. The Nomenclature Committee of International Union of Biochemistry and Molecular Biology (NC-IUBMB) groups the enzymes according to their catalyzing reactions into six classes and provides them with Enzyme Commission (EC) numbers: oxidoreductases (EC 1), transferases (EC 2), hydrolases (EC 3), lyases (EC 4), isomerases (EC 5), and ligases (EC 6). Furthermore, the NC-IUBMB classifies all enzymes into 67 subclasses and 294 sub-subclasses.³

The class of transferases are named as such because they transfer specific functional groups (mainly acyl, amino, glycosyl, methyl, or phosphate groups) from one substance to another. Based on the EC nomenclature, transferases are grouped into 10 subclasses. The two most clinically important subclasses are "transferases transferring nitrogenous groups" (EC 2.6), which is grouped into four further sub-subclasses (including transaminases, EC 2.6.1) and "acyltransferases" (EC 2.3), which is furthermore grouped into three sub-subclasses (including aminoacyltransferases, EC 2.3.2).³

In clinical medicine, the three most relevant transferases are aspartate transaminase (AST; also known as aspartate aminotransferase, [AspAT, ASAT, AAT], serum glutamic oxaloacetic transaminase [SGOT]), alanine transaminase (ALT; also known as alanine aminotransferase, [ALAT] serum glutamate-pyruvate transaminase, serum glutamic-pyruvic transaminase [SGPT]), and gamma-glutamyl transferase (GGT; also known as gamma-glutamyl transpeptidase [GGTP], γ -glutamyl transferase, gamma-GT). AST (EC 2.6.1.1) and ALT (EC 2.6.1.2) belong to the sub-subclass of transaminases (EC 2.6.1). Transaminases transfer amino and keto groups between amino acids and keto acids. AST catalyzes this interconversion between aspartate (amino acid) and α -ketoglutarate (keto acid) on one side and oxaloacetate (keto acid) and glutamate (amino acid) on the other. ALT catalyzes this interconversion between L-alanine (amino acid) and α -ketoglutarate (keto acid) on one side and pyruvate (keto acid) and L-glutamate (amino acid) on the other.³

While AST is found in nearly all human tissues, including, in decreasing order of concentration, liver, cardiac and skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes, ALT is found primarily in the liver. Consequently, AST/ALT ratio is considered as a clinical biomarker for hepatocellular damage. In general, ratios of > 2.0 have a greater association with alcohol hepatitis or non-hepatic tissue damage (e.g., muscle trauma, myocardial infarction), whereas ratios of < 1.0 are often seen among patients with hepatocellular damage (e.g., viral hepatitis, ischemic necrosis of liver, toxic hepatitis).⁴

GGT (EC 2.3.2.2) belongs to the sub-subclass of aminoacyltransferases (EC 2.3.2). Aminoacyltransferases transfer acyl groups between amino acids and peptides. GGT catalyzes the transfer from a 5-L-glutamyl-peptide and an amino

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acid on one side to a peptide and a 5-L-glutamyl amino acid on the other. Even GGT, though found in many human tissues, mainly in kidney, liver, pancreas, spleen, intestine, heart, and brain, its acute elevated serum concentration is linked with acute liver damage, cholestasis, and pancreatitis.⁴

In addition, elevated values of these three transferases are also described in patients with infectious diseases (IDs), principally among those with viral hepatitis, but also among those with other viral (e.g., infections with several virus of the genus of the family *Bunyaviridae* and *Flaviviridae*, infectious mononucleosis, infection with human cytomegalovirus [CMV], herpes simplex, coxsackie virus infection, infection with human immunodeficiency virus [HIV], influenza, and lassa fever), bacterial (e.g., borreliosis, brucellosis, *Chlamydia* infection, legionellosis, leptospirosis, Q fever, rickettsiosis, and syphilis), and protozoan (e.g., amebic liver abscess, malaria, and toxoplasmosis) IDs.⁴⁻⁶

As the majority of these IDs are endemic or typical for tropical and subtropical regions, travelers going to such destinations are particularly at risk of acquiring these IDs.⁷ Data on this subject are rare and no systematic study on infection-induced elevated values of clinically relevant transferases 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 626 million in 1999, and to 1,133 million in 2014. In addition to the traditional favorite destinations of Europe and North America, many new destinations have emerged, especially in tropical and subtropical countries.⁸ Between 2005 and 2014, the average annual growth in international travels worldwide was 4.4%, with highest growth in south Asia (8.6%), in southeast Asia (7.9%), and in sub-Saharan Africa (6.2%). In 2014, about 18.2 million individuals traveled from Germany to destinations outside of Europe. Out of them, 1.5 million traveled to Latin America, 2.8 million to Africa, and 7.8 million to Asia.⁹

The aim of this controlled cross-sectional study was to assess the clinical validity of the laboratory values of clinically relevant transferases such as AST, ALT, and GGT, 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 1999 and 2014 after being in the sub-/tropics. These 14,559 diseased returned travelers (cases) were diagnosed and treated at a single study site, with an additional sample of 1,536 healthy individuals of German origin who had not recently traveled to the sub-/tropics (controls). Consequently, all cases and controls were subject to the same standardized process, allowing for maximal comparability of the data.

MATERIALS AND METHODS

Database. A database from the DITM has been collecting all sociodemographic (gender, age, origin, occupation), travel (duration of travel, destination, type of travel), clinical history and symptoms, diagnostics, and—if applicable—diagnosis data of individuals consulting its outpatient department for treatment or medical checkup. From January 1999 to December 2014, DITM registered 38,059 individuals with complete data sets. Out of them, 22,588 (59.35%) individuals had symptoms after traveling to the sub-/tropics (Latin America, Africa,

or Asia), 7,514 (19.74%) individuals did not have symptoms and had not recently traveled to the sub-/tropics, 4,810 (12.64%) individuals had symptoms but had not recently traveled to the sub-/tropics, and 3,147 (8.27%) individuals did not have symptoms after traveling to the sub-/tropics. The symptoms presented here are those from patients' first consultation at DITM after being in the sub-/tropics.

Study design. In this study, all patients consulted the DITM, at which time the data of the independent (exposure as sociodemographics and travel) and dependent variables (outcomes as symptoms, diagnostics, and diagnosis) were assessed simultaneously: transversal study or cross-sectional study. The data of the dependent variables were not influenced by the study design: noninterventive or observant study. The descriptive part of the study comprised the calculation of the prevalence of elevated values of AST, ALT, and GGT of imported IDs among cases and controls: prevalence study. The analytical part of the study contained a comparison of these prevalences among cases with certain IDs and additionally with those of the controls: controlled study.

Study population: cases and controls. Of the 22,588 patients returning from traveling in the sub-/tropics, 19,581 (86.69%) were of German origin (defined as born in Germany). Among them, 14,559 (74.35%) full data sets with the values of the three clinically relevant transferase enzymes AST, ALT, and GGT, were available. In this study, these 14,559 patients were defined as cases. Out of the second group with 7,514 healthy individuals who consulted the DITM for medical checkup before travel and had not traveled before to the sub-/tropics, 6,481 (86.25%) were of German origin. Among them, 1,536 (23.70%) full data sets with the values of AST, ALT, and GGT, were available. In this study, these 1,536 individuals were defined as controls (Table 1).

Laboratory analysis. Blood samples were taken from all individuals at first visit to the DITM prior to any therapeutic drug administration. Samples collected in S-Monovette[®], serum gel with clotting activator coated tubes (Sarstedt, Nümbrecht, Germany). Generally, the serum was not stored longer than 8 hours under permanent cooling at +2°C to +8°C, and without any freezing. The enzyme kinetics were analyzed exclusively on the same day of blood taking by applying ultraviolet light spectrometry with AU 5800 (Beckman Coulter, Brea, CA).

Reference range. The reference ranges of these enzyme values were defined according to in-house standards of the DITM.¹⁰ Reference ranges for AST: < 92 enzyme units per liter (u/L) serum (for individuals aged 1–23 months [m]), < 55 u/L (2–5 years [y]), < 50 u/L (6–14 y), < 35 u/L (females, > 14 y), < 50 u/L (males, > 14 y). Reference ranges for ALT: < 44 u/L (1 m to 14 y), < 35 u/L (females, > 14 y), < 50 u/L (males, > 14 y). Reference ranges for GGT: < 32 u/L (5 m to 10 y), < 24 u/L (11–15 y), < 40 u/L (females, > 15 y), < 60 u/L (males, > 15 y).

Infectious diseases. The study detected 33 imported IDs with a sample size of more than seven cases of each defined ID: 10 viral, 6 bacterial, 10 protozoan, 6 helminthic, and 1 ectoparasitic IDs. These 33 IDs comprised 3,525 laboratory-confirmed cases with complete data sets. Only exactly defined IDs with laboratory confirmation were considered in this study. Clinically suspected or probable cases were not included (Table 1).

TABLE 1

Normal and elevated values of three clinically relevant transferases (aspartate transaminase, alanine transaminase, and gamma-glutamyl transferase) induced by imported infectious diseases among 14,559 diseased German travelers returning from the tropics and subtropics (cases)

Class	Transferases (EC 2)												Total (%): Normal + elevated values
	Transaminases (EC 2.6.1)				ALT (EC 2.6.1.2)				GGT (EC 2.3.2.2)				
	AST (EC 2.6.1.1)		Transaminases (EC 2.6.1)		Elevated		More than 2-fold elevated		Normal		Elevated		
Cases	13,428	1,131	274	12,607	1,952	518	13,099	1,460	495	14,559	1,460	495	14,559
%	92.23	7.77	1.88	86.59	13.41	3.56	89.97	10.03	3.40	100	10.03	3.40	100
95% CI	91.80-92.67	7.33-8.20	1.66-2.10	86.04-87.15	12.85-13.96	3.26-3.86	89.48-90.46	9.54-10.52	3.11-3.69	100	9.54-10.52	3.11-3.69	100
Controls	1,475	61	6	1,374	162	23	1,361	175	54	1,536	175	54	1,536
%	96.03	3.97	0.39	89.45	10.55	1.50	88.61	11.39	3.52	100	11.39	3.52	100
95% CI	95.05-97.01	2.99-4.95	0.08-0.70	87.92-90.99	9.01-12.08	0.89-2.10	87.02-90.20	9.80-12.98	2.59-4.44	100	9.80-12.98	2.59-4.44	100
Total of 33 IDs	3,052	473	126	2,871	654	202	3,191	334	117	3,525	334	117	3,525
%	86.58	13.42	3.57	81.45	18.55	5.73	90.52	9.48	3.32	100	9.48	3.32	100
95% CI	85.46-87.71	12.29-14.54	2.96-4.19	80.16-82.73	17.27-19.84	4.96-6.50	89.56-91.49	8.51-10.44	2.73-3.91	100	8.51-10.44	2.73-3.91	100
Number of IDs with significantly larger proportions of elevated values of transferases compared with those of all cases (%)	NA	10	5	NA	10	6	NA	5	3	NA	5	3	NA
IDs with significantly larger proportions of elevated values of transferases compared with those of all cases (%)	NA	Hepatitis A (100)	Hepatitis A (100)	NA	Hepatitis A (100)	Hepatitis A (100)	NA	Hepatitis A (100)	Hepatitis A (100)	NA	Hepatitis A (100)	Hepatitis A (100)	NA
	NA	CMV infection (76.92)	CMV infection (46.15)	NA	CMV infection (80.77)	CMV infection (65.38)	NA	Infectious mononucleosis (70.59)	Infectious mononucleosis (57.69)	NA	Infectious mononucleosis (70.59)	Infectious mononucleosis (47.06)	NA
	NA	Chronic hepatitis C (66.67)	Infectious mononucleosis (47.06)	NA	Infectious mononucleosis (76.47)	Infectious mononucleosis (58.82)	NA	Chronic hepatitis C (66.67)	CMV infection (26.92)	NA	Rickettsiosis (20.00)	CMV infection (26.92)	NA
	NA	Infectious mononucleosis (64.71)	0	NA	Cyclosporiasis (65.79)	0	NA	Cyclosporiasis (65.79)	0	NA	Dengue fever (18.55)	0	NA
	NA	Typhoid fever (50.00)	0	NA	Typhoid fever (50.00)	0	NA	Typhoid fever (50.00)	0	NA	0	0	NA
	NA	Cyclosporiasis (44.74)	0	NA	Dengue fever (35.08)	0	NA	Dengue fever (35.08)	0	NA	0	0	NA
	NA	Dengue fever (43.15)	Dengue fever (12.10)	NA	Malaria (26.88)	0	NA	Malaria (26.88)	0	NA	0	0	NA
	NA	Paratyphoid fever (41.67)	0	NA	Rickettsiosis (24.29)	0	NA	Rickettsiosis (24.29)	0	NA	0	0	NA
	NA	Malaria (20.43)	Malaria (11.83)	NA	Giardiasis (20.15)	0	NA	Giardiasis (20.15)	0	NA	0	0	NA
	NA	Rickettsiosis (20.00)	0	NA	0	0	NA	0	0	NA	0	0	NA

ALT = alanine transaminase; AST = aspartate transaminase; CI = confidence interval; CMV = cytomegalovirus; EC = Enzyme Commission number; GGT = gamma-glutamyl transferase; NA = not applicable. In this controlled cross-sectional study, 1,536 healthy Germans without having recently traveled to the tropics and subtropics served as controls.

Data analysis. The database of the DITM was the source of all data analyzed in this study. The descriptive analysis was performed by Excel Worksheet (Microsoft, Redmond, WA). The proportions of lymphocytosis and lymphopenia with 95% confidence intervals were used to assess significant differences between cases and controls, and between cases with certain IDs. Bivariate approximative tests (χ^2 tests) and exact test (Fisher's tests) were conducted using EpiInfo, version 3.3.2. (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.

Ethical considerations. Ethical clearance for the study protocol was provided by the Ethical Committee of the Medical Faculty at the Medical Center of 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. The study population comprised 14,559 cases and 1,536 controls who fulfilled the inclusion criteria. Among the cases, 52.42% (7,632) were females, whereas this proportion was significantly (*P* < 0.01) lower among the controls (37.96%; 583). Among the cases, the age range was 10 m to 92.8 y, with a median of 34.5 y, and an interquartile range (IQR) of age was 27.0–47.1 y. Among the controls, the age range was 15 m to 92.6 y, the median age was 38.1 y, and the IQR was 29.0–49.2 y. Grouped into the age groups of 0–19 y, 20–64 y, and 65–92 y, the corresponding proportions among the cases were 4.70% (684), 89.95% (13,096), and 5.35% (779), respectively, and among controls 8.20% (126), 86.26% (1,325), and 5.53% (85) (Table 1).

Transferases values among cases and controls. The proportion of elevated values for AST among cases (7.77%), among female cases (8.91%), among male cases (6.51%), and among cases of age 20–64 y (7.74%) were significantly larger than those among controls (3.97%), among female controls (5.49%), among male controls (3.04%), and among controls of age 20–64 y (3.85%), respectively (Table 1).

The proportion of elevated values for ALT among cases (13.41%), among female cases (11.82%), and among cases of age 20–64 y (13.79%) were significantly larger than that among controls (10.55%), among female controls (5.49%), and among controls of age 20–64 y (13.79%), respectively (Table 1).

The proportion of elevated values for GGT among cases (10.03%) were not significantly different from that of controls (11.39%), whereas among cases of age 0–19 y (6.73%), this proportion was significantly larger than that among controls of age 0–19 y (0.79%) and among cases of age 65–92 y (17.84%), this proportion was significantly lower than that among controls of age 65–92 y (32.94%) (Table 1).

Transferases values and travel data. Among the 14,559 cases, the range of travel duration was 1 day to 50 y, with a median of 21 days, and an IQR of 14–42 days. The proportions of elevated values of AST and of ALT were not significantly different among cases with travel duration of 1–14 days (7.03% and 13.76%, respectively), 15–30 days

(8.44% and 13.62%, respectively), and < 30 days (7.73% and 12.71%, respectively). The proportions of elevated values of GGT were larger among cases with travel duration of 1–14 days (11.44%) and 15–30 days (10.60%) and were significantly larger for > 30 days (7.63%).

Among the 14,559 cases, 7,270 (49.93%) traveled to Asia, 4,574 (31.42%) to Africa, and 2,715 (18.65%) to Latin America. The proportions of elevated values of AST were not significantly different between cases with travel destination in Asia (8.49%), Africa (7.13%), and Latin America (6.92%). The proportion of elevated values of ALT were significantly larger among cases with travel destinations in Asia (14.25%) and in Africa (12.77%) than among those in Latin America (7.31%). The proportion of elevated values of GGT were significantly larger among cases with travel destination in Africa (11.02%) than among those in Latin America (8.88%).

Among 14,559 cases, 7,854 (53.95%) were backpackers, 2,876 (19.75%) were all-inclusive travelers, 1,765 (12.12%) were business travelers, and 2,064 (14.18%) were classified among "other types of travel." The proportions of elevated values of AST were not significantly different between backpackers (8.05%), all-inclusive travelers (7.48%), business travelers (7.20%), and cases with other types of travel (7.61%). The proportion of elevated values of ALT were significantly larger among cases with other types of travel (19.38%) than among backpackers (13.08%), all-inclusive travelers (13.84%), and business travelers (7.20%). The proportion of elevated values of GGT were significantly larger among all-inclusive travelers (12.87%) than among backpackers (9.15%) and among cases with other types of travel (8.77%).

Transferases values and symptoms. In the database, 15 different symptoms were systematically registered. The most documented symptoms were diarrhea (43.75%), fever (30.48%), nausea (20.57%), skin disorders (14.77%), and arthralgia (12.91%). The proportion of elevated values of AST and ALT were significantly larger among cases with fever (12.84% and 17.78%) and with arthralgia (10.80% and 17.34%) than among those with diarrhea (7.13% and 13.27%), nausea (8.25% and 13.52%), and skin disorders (8.23% and 13.67%). The proportion of elevated values of GGT were significantly larger among cases with fever (14.24%) and with arthralgia (14.31%) than among those with diarrhea (8.09%) and nausea (7.68%), but not compared that among cases with skin disorders (11.95%).

Frequently imported infectious diseases. In the study population, 31 IDs with more than seven laboratory confirmed cases of each ID with known values of AST, ALT, and GGT were documented. Among the 13 most frequent IDs with more than 40 reported cases, six were intestinal infections: with *Blastocystis* (861 cases), *Giardia* (660), *Campylobacter* (553), *Shigella* (202), *Salmonella* (199), and *Entamoeba* (115) spp. The remaining seven frequently documented IDs were dengue fever (248), malaria (93), cutaneous larva migrans (73), rickettsiosis (70), infectious mononucleosis (51), cryptosporidiosis (52), and schistosomiasis (49).

IDs with largest proportions of elevated values of transferases. This study assessed IDs with significantly larger proportions of elevated values of AST (hepatitis A [100%], CMV infections [76.92%], chronic hepatitis C [66.67%], infectious mononucleosis [64.71%], typhoid fever [50.00%], cyclosporiasis [44.74%], dengue fever [43.15%], paratyphoid fever

[41.67%], malaria [20.43%], and rickettsiosis [20.00%]), of ALT (hepatitis A [100%], CMV infection [80.77%], infectious mononucleosis [76.47%], chronic hepatitis C [66.67%], cyclosporiasis [65.79%], typhoid fever [50.00%], dengue fever [35.08%], malaria [26.88%], rickettsiosis [24.29%], and giardiasis [20.15%]), and of GGT (hepatitis A [100%], infectious mononucleosis [70.59%], CMV infection [57.69%], rickettsiosis [20.00%], and dengue fever [18.55%]), compared with the proportions of all cases (Table 1).

IDs with largest proportions of more than 2-fold elevated values of transferases. This study assessed IDs with significantly larger proportions of more than 2-fold elevated values of AST (hepatitis A [100%], CMV infections [46.15%], infectious mononucleosis [47.06%], and dengue fever [12.10%]), of ALT (hepatitis A [100%], CMV infection [65.38%], infectious mononucleosis [58.82%], cyclosporiasis [15.79%], dengue fever [16.13%], and malaria [10.75%]), and of GGT (hepatitis A [75.00%], infectious mononucleosis [47.06%], and CMV infection [26.92%]), compared with the proportions of all cases (Table 1).

DISCUSSION

This study is the largest controlled cross-sectional study, which assessed the clinical validity of the laboratory values of AST, ALT, and GGT induced by imported IDs. The data derived from 14,559 diseased German travelers seeking treatment or medical checkup at the outpatient travel clinic of the DITM of the Medical Center of the University of Munich, after returning from tropical and sub-tropical countries in Latin America, Africa, and Asia. The controls were 1,536 healthy German individuals without having recently traveled to the sub-/tropics.

The overall results of the study showed significantly larger proportions of elevated values of AST and of ALT among cases compared with those among controls. This finding was expected as nine imported IDs with specific hepatitis (hepatitis A and chronic hepatitis C) or systemic infections (CMV infection, infectious mononucleosis, typhoid fever, dengue fever, malaria, and rickettsiosis) were found in this study, causing significantly larger proportions of elevated values of AST and of ALT. Furthermore, a significantly larger proportion of elevated values of AST were seen among patients with paratyphoid fever, whereas of ALT, this was found among those with giardiasis.

In contrast to the transaminases, the overall proportions of elevated values of GGT between cases and controls were not significantly different. In this study, only five IDs (hepatitis A, infectious mononucleosis, CMV infection, rickettsiosis, and dengue fever) were found to be associated with elevated values of GGT.

Sex- and age-related normal values of AST, ALT, and GGT are known and were considered in this study by comparing the proportions of elevated values among different populations, instead of comparing absolute values of these enzymes. Nevertheless, this study assessed significant associations between these independent variables (sex, age) and the proportions of elevated values, but most of these associations were confounded by IDs.

The significantly larger proportions of elevated values of ALT among cases were only seen among females. This finding was confounded by the large proportion (62%) of females

among the cases with CMV infection. After acute hepatitis A, more than 80% of the cases with CMV infections were diagnosed with significantly larger proportion of elevated values of ALT.

For both transaminases, significantly larger proportions of elevated values among cases (compared with those among controls) were found only in age group 20–64 y. This finding was confounded by dengue fever and giardiasis. These two IDs presented the highest number of these cases with elevated values of AST and ALT, but also large proportions of patients in age group 20–64 y: 91% among patients with dengue fever and 93% among those with giardiasis. In contrast to that, a significantly larger proportion of elevated values of GGT among cases (compared with those among controls) were found only in age group 0–19 y. This finding was confounded by infectious mononucleosis and hepatitis A. Patients with one of these two IDs presented the largest proportion (hepatitis A: 100%; infectious mononucleosis: 70%) of elevated values of GGT, but also large proportions of patients in age group 0–19 y: 22% among patients with infectious mononucleosis and 13% among those with hepatitis A.

Fever and arthralgia, as typical manifestations of systematic infections, have shown significantly larger proportions of elevated values of all three transferases, whereas these laboratory findings were not seen among patients suffering by diarrhea, nausea, or skin disorders. This finding was mainly caused by three viral IDs (dengue fever, infectious mononucleosis, and CMV infection), as each of them presented large proportions of patients with fever (> 81%) and a high number of elevated values of all three transferases. Furthermore, dengue fever was the ID with the largest proportion of arthralgia (45%), followed by other mainly febrile IDs such as hepatitis A (25%), rickettsioses (23%), malaria (22%), and typhoid fever (21%).

In addition, this study found significant associations between independent variables concerning travel (duration, destination, and type of travel) and the proportions of elevated values of transferases, but these associations were highly confounded by IDs as well. Significantly, larger proportions of elevated values of ALT were found in travelers with destinations in Africa and Asia. For travelers to Africa, this finding was confounded by rickettsiosis and malaria (94% and 78%, respectively). Both IDs presented large proportions of elevated values of ALT (24% and 27%, respectively). For travelers to Asia, this finding was confounded by dengue, chronic hepatitis C, typhoid fever, and cyclosporiasis (> 70% each). All these IDs presented large proportions of elevated values of ALT: > 35%. The significantly higher proportion of elevated values of AST and ALT among cases with cyclosporiasis, who had mainly (> 76%) traveled to Asia, remained unclear in this study. Data analysis did not find any confounding, which might explain these results. Finally, it can be assumed that biliary diseases caused by *cyclospora* infection, particularly cholangitis or unspecific hepatitis, had led to elevated values of transaminases.

Significantly, larger proportions of elevated values of GGT were found in travelers with destinations in Africa, for all-inclusive travelers, and for those with short travel durations of 1–30 days. For Africa, this finding was confounded by rickettsiosis, which presented a large proportion of elevated values of GGT (20%). For all-inclusive travelers, it can be assumed that this finding was confounded by CMV infection,

which presented the largest proportion (27%) of all-inclusive travelers among all IDs listed here. More than 57% of the patients with CMV infections were diagnosed with elevated values of GGT. For the duration of 1–30 days, this finding was also confounded by rickettsiosis and CMV infection. Patients with these two IDs were traveling for during shorter durations than patients with other IDs. Although patients with rickettsiosis or CMV infection reported to have traveled in 88% and 81%, respectively during 1–30 days, the corresponding overall proportion among all patients was 71%. In contrast to ALT and GGT, for AST, no significantly larger proportion of elevated values were found after comparing with the variables concerning travel (duration, destination, and type of travel).

Regardless of the different findings for AST, ALT, and GGT, the largest proportions of very elevated values (at least 2-fold elevation) were found for hepatitis A, CMV infection, and infectious mononucleosis of all three transferases. Furthermore, these three IDs were also among those with the highest number of cases with elevated values for all three transferases.

This study has some limitations. It has a cross-sectional design, and as such, all data on independent (demographics, travel, and symptoms) and dependent variables (sampling specimens for laboratory diagnostics and diagnosis of IDs) were collected for each patient at the same day of consultation at the DITM. Consequently, the causal interpretation of assessed associations between independent and dependent variables is limited. Furthermore, data on the clinical status before travel were not collected from all patients, as in some cases it was not clinically relevant. Therefore, unknown liver comorbidities could have influenced the results and may have been unbalanced between the groups.

As no regular follow-up of patients was performed after consulting the DITM, no data on duration of symptoms or on symptoms, which developed afterwards, were considered in this study. As no absolute data on the number of travelers were available, no exact calculations on relative risk of a certain imported ID could be estimated. In addition, the great majority of cases presented here were diagnosed during routine work at the outpatient travel clinic of the DITM, consequently many elaborate laboratory tests were not performed if not clinically relevant. For example, biomolecular testing of norovirus, rotavirus, or *Escherichia* spp. among patients with diarrhea was not routinely performed, as no absolute consequence for treatment can be drawn out of the exact diagnosis. Among the cases with intestinal infections with *Blastocystis hominis*, a significantly larger proportion of elevated values of AST were found. This association was not assumed to be causal, but probably confounded by enteric pathogens, as *B. hominis* may only serve to complement other enteric pathogens by causing diarrhea. Finally, an overall limitation concerning the detection of enzymes among patients with a certain disease is the time of blood withdrawal after onset of symptoms, which was not considered in the study. For example, for dengue, there is a strong association between the duration of symptoms and the proportion of elevated values of transferases. In this study, approximately 72% of the dengue patients consulted the DITM between day 1 and day 7 after onset of symptoms. In this early stage, the level of transferases has not reached their highest values, which are expected on day 9 or day 10.

However, as all patients were subject of the same standardized process, maximal comparability of the data was possible in this study. The study population was restricted to travelers of German origin, as enzyme values may vary immensely between different international populations, especially those living in regions endemic for certain IDs. Consequently, the conclusions taken out of this study are restricted to German travelers.

CONCLUSION

The proportion of elevated values of the transferases AST, ALT, and GGT were significantly associated with certain variables concerning demographics (sex, age), travel (duration of travel, destination, type of travel), and symptoms of patients. However, these associations were highly confounded by several IDs, imported by diseased German travelers. The study demonstrates that the determination of AST and ALT among travelers returning from the sub-/tropics has a high clinical validity, as their elevated values are typically caused by several imported viral (mainly hepatitis A, CMV infections, chronic hepatitis C, infectious mononucleosis, and dengue fever), bacterial (mainly typhoid fever and rickettsiosis), and protozoan (mainly cyclosporiasis and malaria) IDs. As the proportion of elevated values of GGT were not seen among patients with any other imported ID, no additional clinical validity was found by the determination of GGT.

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