

Meningitis gone viral: Description of the German Echo Wave 2013

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Abstract

BACKGROUND: Aseptic meningitis epidemics may pose various health care challenges. **OBJECTIVE:** We describe the German enterovirus meningitis epidemics in the university hospital centers of Düsseldorf, Cologne and Berlin between January 1st and December 31st, 2013. **RESULTS:** A total of 72 enterovirus (EV-positive) meningitis cases were detected in our multicenter cohort, corresponding to 2.1% of all EV-positive cases which were voluntarily reported within the National Enterovirus surveillance (based on investigation of patients with suspected aseptic meningitis/encephalitis and acute flaccid paralysis) by physicians within this period of time. Among these 72 patients, 38 (52.8%) were echovirus-positive (18 pediatric and 20 adult cases, median age 18.5 years). At the same time, 45 aseptic meningitis cases in our cohort were excluded to be due to enteroviral infection (EV-negative). Three EV-negative patients were tested positive for varicella zoster virus (VZV) and one EV-negative patient for herpes simplex virus 2. Hospitalization was significantly longer in EV-negative cases. Cerebrospinal fluid analysis did not reveal significant differences between the two groups. After discharge, EV-meningitis resulted in significant burden of sick leave in our pediatric cohort as parents had to care for the children at home. **CONCLUSION:** Voluntary disease-specific surveillance, such as provided by the National Enterovirus surveillance in our study may be a valuable tool for epidemiological research.

Background

Periodic aseptic meningitis epidemics can be a challenge in patient- and health care. A large retrospective analysis of a US-American cohort revealed that in 21% of cases the etiology of aseptic meningitis remains unknown¹. Aseptic meningitis is defined² by an inflammation of the leptomeninges in which the causative agent cannot be identified by cerebrospinal fluid culture³. Viruses are the most common causes of this disease^{1,3}. Most viral meningitides are caused by enteroviruses⁴. These belong to the Picornaviridae consisting of species A-D, and comprise the subtypes of coxsackieviruses, polioviruses, echoviruses and certain enterovirus serotypes. The infection occurs usually via fecal-oral route, but also infestation of the respiratory tract and a droplet infection are possible. Interestingly, in previous studies, adults were more likely to be tested positive for herpes simplex virus and West Nile virus while children were more likely to be tested positive for enterovirus (EV)⁵. Therefore, multiple studies have been conducted in order to better understand this phenomenon: In a Danish nation-wide prospective observational study between 1st of January 2015 to 30th of June 2016 an unfavorable outcome of viral meningitis was documented in 17% of all patients⁶. According to a UK study, the infection rates of viral meningitis are mainly driven by an EV predominance of echovirus 307. EV meningitis epidemics in Shandong, (People's Republic of China, 2014⁸) and Finland (2009 and 2010⁹) and the clinical pattern of viral central nervous system (CNS) infections in Italy¹⁰ have previously been characterized: EV-positive patients presented with fever, nausea and vomiting, were most likely to be children, and had no clear gender predominance. In addition to antipyretic and analgesic therapy for temperature control, pleconaril, an inhibitor of enteroviral replication, is available. However, it was not approved in Europe, as a placebo-controlled double-blind study demonstrated only a moderate effect of the drug¹¹. In particularly severe

cases, administration of immunoglobulins also had a positive effect on the course of the disease¹². Cerebrospinal fluid (CSF) and clinical features of EV-positive meningitis patients in Germany¹³ and the differences in adult and pediatric EV-positive meningitis patients in Switzerland¹⁴ have already been analyzed, but there is still a paucity of data describing the differences in EV-positive meningitis and EV-negative meningitis patients.

Patients And Methods

We conducted a retrospective chart review study at the Departments of Neurology of the Heinrich-Heine University Düsseldorf, the University Hospital of Cologne, the Charité – Universitätsmedizin Berlin and the Department of General Pediatrics, Neonatology and Pediatric Cardiology of the Heinrich-Heine University Düsseldorf searching for all patients with aseptic CNS infection in 2013. The study was approved by the ethics committee, University of Düsseldorf (registry number 4423). We used ICD-10 codes to identify cases of interest. As such, priority was given to the ICD-10 keys A87 and G02 (Table 1). However, as patient data may not have been in the categories listed above due to less precise encryption despite manifest illness, a wider query was additionally performed to identify all patient data encoded as A85-A89 (Other viral encephalitis, not elsewhere classified; Unspecified viral encephalitis; Viral meningitis; Other viral infections of central nervous system, not elsewhere classified; Unspecified viral infection of central nervous system, Table 1) and G02-05 (Meningitis in other infectious and parasitic diseases classified elsewhere; Meningitis due to other and unspecified causes; Encephalitis, myelitis and encephalomyelitis; Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere, Table 1). Virological testing was performed in a standardized manner by the National Reference Laboratory for Poliomyelitis and Enteroviruses. Case definition After the above-mentioned identification of patient data, the patient records were individually evaluated to exclusively select cases of aseptic meningitis defined according to the Centers for Disease Control and Prevention (CDC)¹⁵ as acute onset of meningeal symptoms, fever, cerebrospinal fluid pleocytosis with bacteriologically sterile cultures. Analysis The following criteria were investigated for further analysis: Patient age, time point of manifestation, prehospital time / duration of clinical manifestation before confirmation of aseptic meningitis by CSF analyses, results of CSF diagnostics (cell count, protein content), duration of inpatient stay, type of clinical restitution (complete restitution vs. persistence of residual symptoms), for children treated in Düsseldorf time of incapacity for work of parents. In order to put this data in perspective, we performed a query of the German-wide database of the Robert Koch Institut (RKI; EVSurv)¹⁶ of all EV-positive meningitis cases in 2013. Data was obtained in the context of the National Enterovirus surveillance, which is based on voluntary reporting and investigation of hospitalized patients with suspected aseptic meningitis/encephalitis and acute flaccid paralysis. Statistical analyses were performed as indicated using SPSS Version 20 (IBM Corp. NY, USA); non-parametric testing was performed since all investigated variables were non-normally distributed (Shapiro-Wilk-test); p values <0.05 were considered significant. If not specified otherwise, data are provided as median (25th; 75th percentile). Furthermore, a Chi-Square-test was performed in order to compare adults with children and a Spearman's correlation was performed in order to explore predictors of hospitalization. Adjusted p-values (adj. p) were calculated using

Bonferroni correction, values below 0.05 were considered significant. To enhance readability of the results section, significant values are provided in three categories: < 0.05, < 0.01, and < 0.001, respectively. Finally, a multivariate, stepwise linear regression was performed in order to extract variables of potential predictive value for the time of hospitalization.

Results

Results of the retrospective analysis in Düsseldorf, Cologne and Berlin 2013 We identified 72 EV-positive cases (31 females, 41 males) with a median age of 15 (3.25; 32.75) years. Among these 72 patients, 38 (52.8%) were echovirus-positive (18 pediatric and 20 adult cases, median age 18.5 (5.25; 31.25) years), 1 patient was enterovirus 71-positive, 1 patient was coxsackie A9-positive, 1 patient was enterovirus B-positive and the specific enterovirus species of the remaining 31 EV-positive cases remained unknown. Furthermore, we identified 45 enterovirus-negative cases (16 females, 29 males, median age 36 (28; 48.5) years). Among EV-negative cases, three were related to varicella zoster infection, one to herpes simplex 2 and no virus could be identified in the other patients. EV-positive meningitis cases peaked in July/August (Figure 1). Analysis of the CSF parameters cell count (EV-positive: 81 (12; 205) cells/ μ l, EV negative 67 (17.5; 185.25) cells/ μ l, Figure 2A) and total protein (EV-positive 0.52 (0.35; 0.68) g/l, EV-negative 0.53 (0.36, 0.78) g/l, Figure 2B) in EV-positive and EV-negative patients revealed no significant difference (Mann-Whitney U test). 2 EV-positive and 1 EV-negative CSF samples could not be evaluated due to a blood contamination. Analysis of the number of nights spent in hospital by the patients revealed that hospitalization was significantly longer in EV-negative (6 (3; 13) nights) than in EV-positive cases (3 (1; 5) nights, adj. $p < 0.01$, Mann-Whitney U test, Figure 3). No fatal cases occurred. In children, parents reported of mild complaints after discharge like headache, backache and fatigue for 0 to 7 days (median 2 days; Düsseldorf cohort). After discharge, one of the parents had to care for the children at home (0 to 5 days, median 3 days; Düsseldorf cohort). Adults vs. children A significantly higher ratio of children was found in the enterovirus-positive cohort, compared to the enterovirus negative group (38/72 vs. 4/45, Chi-Square-test, adj. $p < 0.001$). Children (both EV-positive and EV-negative) had a shorter period of hospitalization (adj. $p < 0.001$) and lower CSF protein levels than adults (adj. $p < 0.001$). There was no significant difference of CSF cell counts (Mann-Whitney U test, respectively). An exclusive analysis of either adults or children did not reveal significant differences between EV-positive and EV-negative patients regarding age, duration of inpatient stay, CSF cell count and CSF total protein (Mann-Whitney U test, respectively). Numerical data of abovementioned comparisons are provided in Table 2. Predictors of hospitalization periods In general, the duration of inpatient stay correlated with age (Spearman's Rho correlation coefficient 0.418, $p < 0.001$), CSF total protein (Spearman's Rho correlation coefficient 0.319, $p < 0.001$), and the delay from symptom onset to lumbar puncture (Spearman's Rho correlation coefficient 0.232, $p = 0.023$). For nominal variables, enterovirus status ($\eta = -0,32$) correlated with the duration of inpatient stay. In contrast, echovirus status, gender, and location (Neurological center the patient was treated) did not show a relevant correlation with the duration of the inpatient stay ($|\eta| < 0,3$). Finally, a multivariate, stepwise linear regression was performed using the abovementioned variables (age, CSF cell count, CSF protein, delay between symptom onset and spinal tap enterovirus status, echovirus status,

gender, treating center (Berlin, Cologne, Duesseldorf)). A total of three variables (age, CSF protein, and Echovirus status) were kept, which accounted for 30% of the variance of the hospitalization period (adjusted R² = 0.302, standardized Beta values: age = 0.354, CSF protein 0.247, and echovirus status -0.169, respectively). Therapy The cases diagnosed with varicella zoster virus and herpes simplex virus 2 received specific therapy. No child received specific therapy in Düsseldorf. RKI database query An RKI database query (retrieved from <https://survstat.rki.de/>) revealed a total of 3455 EV-positive cases in 2013. 1242 of these cases had positive EV-PCR testing and 672 cases were positive for echovirus-30. Therefore, our study includes 2.1% of the reported EV-positive cases in Germany.

Discussion

The prevalence of enteroviral meningitis is high worldwide (estimated 75,000 cases annually in the United States)¹¹, with the highest rates of infection in the summer and early autumn months (June, July and August; Figure 1). Notably, coxsackie and echoviruses are identified as responsible serotypes. In addition, enteroviruses are also highly neurotropic and are associated with meningitis, meningoencephalitis, poliomyelitis-like anterior myelitis, and Guillain-Barré syndrome^{17,18}. With age, the incidence of enteroviral meningitis decreases. Therefore, the incidence is highest in infants and toddlers¹⁹, which was also the case in our cohorts (Table 2). In adult patients, the disease generally necessitates inpatient treatment for several days²⁰. When children are affected, one parent may be incapacitated for a certain period of time to care for the child. In both cases, the disease may be associated with a temporary inability to work (either patient or parent). Because of the high number of cases per year, considerable costs arise for society due to the loss of work and the necessary resources for medical treatment²¹, although meningitis caused by enteroviruses usually has a relatively benign course. To the best of our knowledge, the economic burden for society due to EV-positive meningitis has not been determined so far; and our data also provide just a limited insight, since we analyzed the duration of inpatient stay but did not assess any further inability to work. Our data indicate that the course of EV-positive meningitis is predominantly benign, and that hospitalization time was significantly shorter in EV-positive, compared to EV-negative cases. This was also the case, when we did not consider the above-mentioned meningitis cases that received specific antiviral therapy (varicella zoster virus, herpes simplex virus 2). Moreover, a higher ratio of affected children and young adults were found in EV-positive cases. This could be explained by affected parents of young, diseased children. Hence, earlier convalescence in EV-positive groups may be explained by differences of age between both groups rather than different courses of the disease in general. Despite the generally excellent outcome of aseptic meningitis, there are rare instances of complicated courses that may lead to persistent neurological disability or even death^{22–25}. Strategies for the systematic containment of endemic diseases are focused on ensuring hygienic measures to prevent the spread of viruses, as some weeks after illness, virulent pathogens can still be excreted via the feces. In agreement with previous studies, enterovirus infections were detected as the most common cause for an aseptic meningitis in our cohort, driven by a high prevalence of echoviruses (75%). Indeed, our study demonstrates that voluntary reporting of diseases such as in this case can be an effective tool to better understand epidemiological details of certain diseases: The mean age of EV-positive patients in

our centers was 15 (3.25; 32.75) years, which accurately fits to previous data of Shandong⁸ and Finland⁹ (Finland 2009 15 years 8 months, Finland 2010 17 years 6 months, Shandong 2014 children within 15 years of age). The mean age of EV-negative pediatric patients (8 (7.25; 14.75) years) in our cohort was quite similar to that in a large South Korean pediatric cohort (8.4 ± 5 years)²⁶.

Conclusion

EV-positive epidemics are similar in terms of age and gender distribution and other factors worldwide. Overall, this entity remains a rather benign form of meningitis. Still, epidemics of all sort are a challenge for the health care system. Therefore, we recommend rigorous testing and reporting of meningitis cases. Within the National Enterovirus surveillance (EVSurv) all pediatric and neurological hospitals in Germany are offered free-of-charge enterovirus diagnostics in patients with suspected aseptic meningitis / encephalitis or acute flaccid paralysis. This health care concept is also well established in the US and led to a concise description of the disease burden²⁷.

Abbreviations

EV Enterovirus VZV Varicella zoster virus CNS Central nervous system CSF Cerebrospinal fluid RKI Robert Koch Institut CDC Centers for Disease Control and Prevention adj. p adjusted p-value

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Tables

Table 1: List of ICD-10 codes utilized to identify patients with aseptic meningitis from the clinical databases of each hospital participating in this study.

ICD-10	Description
A85	Other viral encephalitis, not elsewhere classified
A86	Unspecified viral encephalitis
A87	Viral meningitis
A88	Other viral infections of central nervous system, not elsewhere classified
A89	Unspecified viral infection of central nervous system
G02	Meningitis in other infectious and parasitic diseases classified elsewhere
G03	Meningitis due to other and unspecified causes
G04	Encephalitis, myelitis and encephalomyelitis
G05	Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere

Table 2: Distribution of age, hospitalization, CSF cell count, and CSF protein for EV negative, EV positive, and all patients (Total). All groups are further subdivided by age into adults (ADU), children (PED), and all (Total) patients. N = number of patients, 75th perc. = 75th percentile, 25th perc = 25th percentile.

EV status	Age group	Age (years)	Hospitalization (nights)	CSF cell count (cells/ μ l)	CSF protein (g/l)	
EV negative	ADU	N	41	41	40	40
		Range	64	35.00	1255	1.30
		75 th perc.	50	13	202.25	0.78
		median	36	6	61.5	0.53
		25 th perc.	30	3.5	15.25	0.39
	PED	N	4	4	4	4
		Range	10	5	100	0.64
		75 th perc.	14.75	5	129.75	0.79
		median	8	2	100	0.42
		25 th perc.	7.25	1.25	44.75	0.23
	Total	N	45	45	44	44
		Range	77	35	1255	1.30
		75 th perc.	48.5	13	185.25	0.78
		median	36	6	67	0.53
		25 th perc.	28	3	17.50	0.36
EV positive	ADU	N	34	34	34	34
		Range	56	31.00	744	1.29
		75 th perc.	40	6	314.75	0.80
		median	33.5	4	114.5	0.65
		25 th perc.	24	1.75	40.5	0.48
	PED	N	38	38	36	36
		Range	17	9.00	877	0.73
		75 th perc.	9	3.25	142	0.57
		median	5	2.00	24.5	0.34
		25 th perc.	0	1	6.75	0.25
	Total	N	72	72	70	70
		Range	74	31	877	1.51
		75 th perc.	32.75	5	205	0.68
		median	15	3	81	0.52

		25 th perc.	3.25	1	12	0.35
Total	ADU	N	75	75	74	74
		Range	66	36.00	1255	1.66
		75 th perc. median	44	10	275.75	0.78
		25 th perc. median	36	5	88	0.56
		25 th perc.	27	2	23.75	0.43
	PED	N	42	42	40	40
		Range	17	9.00	877	0.73
		75 th perc. median	9	3.25	132.25	0.58
		25 th perc. median	6	2	34.5	0.36
		25 th perc.	0.75	1	9.5	0.250
	Total	N	117	117	114	114
		Range	84	36	1255	1.65
		75 th perc. median	38	7	196.5	0.74
		25 th perc. median	26	4	78	0.52
		25 th perc.	8	2	15	0.36

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee in Düsseldorf (registry number 4423).

Consent for publication

Due to the retrospective manner of this study, patient consent was waived by the ethics committee.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interest

Jonas Graf* - received travel/meeting/accommodation reimbursements from Biogen, Merck Serono, and Sanofi-Genzyme.

Christian Hartmann* - declares no relevant competing interests.

Helmar C Lehmann - declares no relevant competing interests.

Klemens Ruprecht - received research support from Novartis, Merck Serono and German Ministry of Education and Research as well as speaking fees and travel grants from Bayer Healthcare, Biogen Idec, Merck Serono, sanofi-aventis/Genzyme, Teva Pharmaceuticals, Roche, Novartis, and Guthy Jackson Charitable Foundation.

Michael Karenfort -- received, with approval of the Rector of Heinrich-Heine University and the CEO of University of Düsseldorf Hospital honoraria for consulting, serving on steering committees and speaking from Novartis.

Christian Schneider - declares no relevant competing interests.

Ortwin Adams - declares no relevant competing interests.

Carolin Otto - declares no relevant competing interests.

Hans Martin Bosse - declares no relevant competing interests.

Sabine Diedrich - declares no relevant competing interests.

Sindy Böttcher - declares no relevant competing interests.

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Authors' Contributions:

Jonas Graf* - study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript

Christian Hartmann* - study concept/design, acquisition/analysis/interpretation of data, drafting of the manuscript

Helmar C Lehmann - acquisition/analysis/interpretation of data, revision of the manuscript

Klemens Ruprecht - acquisition/analysis/interpretation of data, revision of the manuscript

Michael Karenfort - acquisition/analysis/interpretation of data, revision of the manuscript

Christian Schneider- acquisition/ analysis of data

Ortwin Adams - critical revision of the manuscript

Carolin Otto - acquisition/analysis/interpretation of data, revision of the manuscript

Hans Martin Bosse - acquisition/analysis/interpretation of data, revision of the manuscript

Sabine Diedrich - acquisition/analysis/interpretation of data, revision of the manuscript

Sindy Böttcher - acquisition/analysis/interpretation of data, revision of the manuscript

Alfons Schnitzler - critical revision of the manuscript

Hans-Peter Hartung - critical revision of the manuscript

Orhan Aktas* - analysis/interpretation of data, and revision of the manuscript

Figures

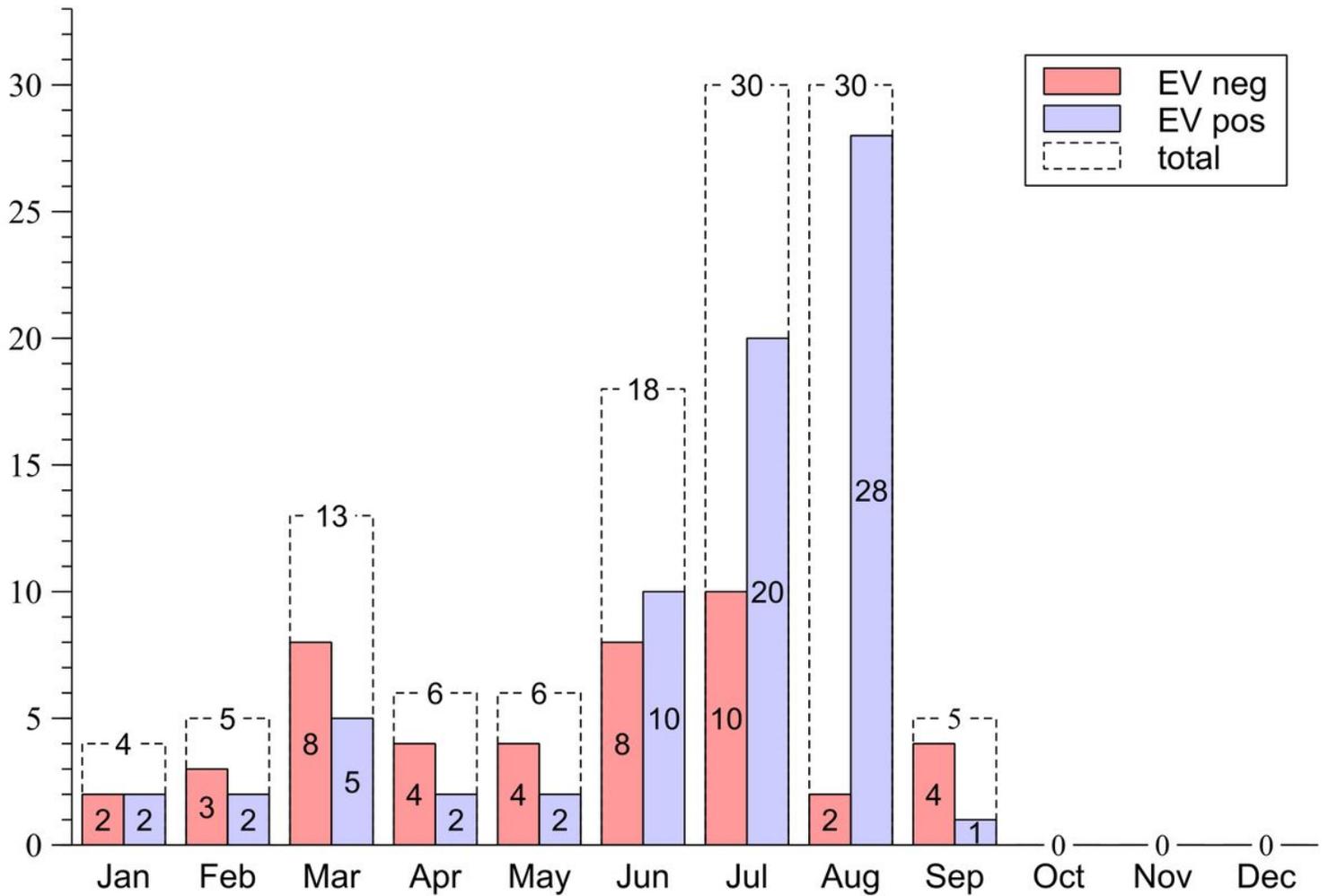


Figure 1

Monthly distribution of meningitis detection in 2013 (Düsseldorf, Cologne, Berlin), as provided from database query. Enterovirus (EV)-positive cases peaked in July/August.

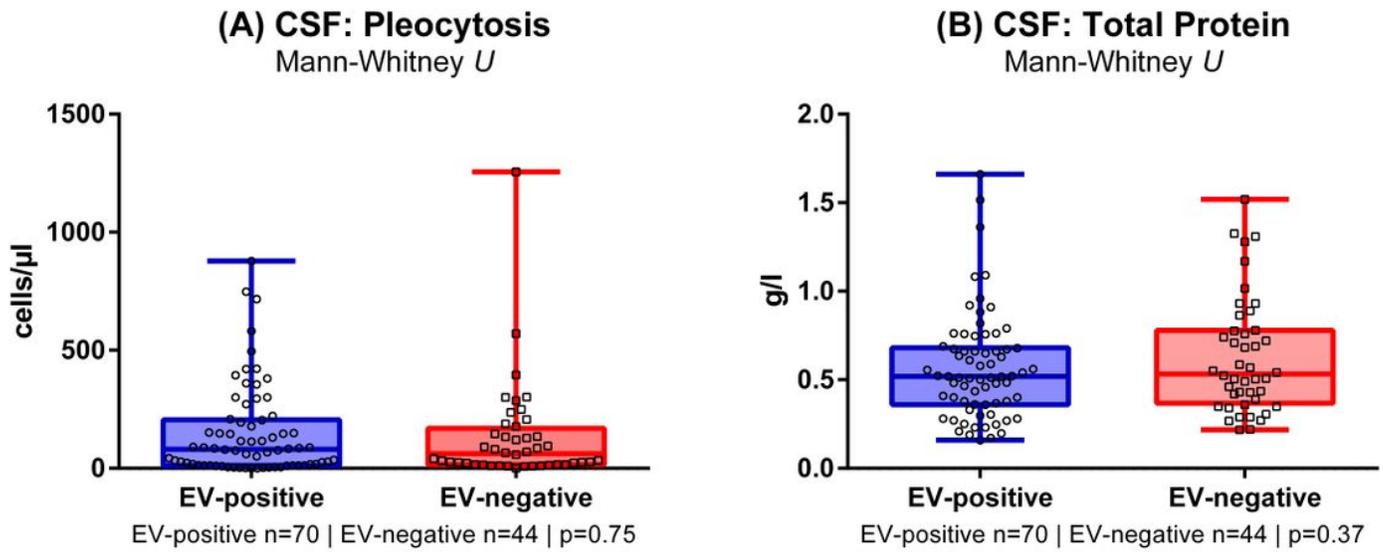


Figure 2

Cerebrospinal fluid analysis of enterovirus (EV)-positive and EV-negative patients. No significant difference in cell count (A) and total protein (B). CSF = cerebrospinal fluid.

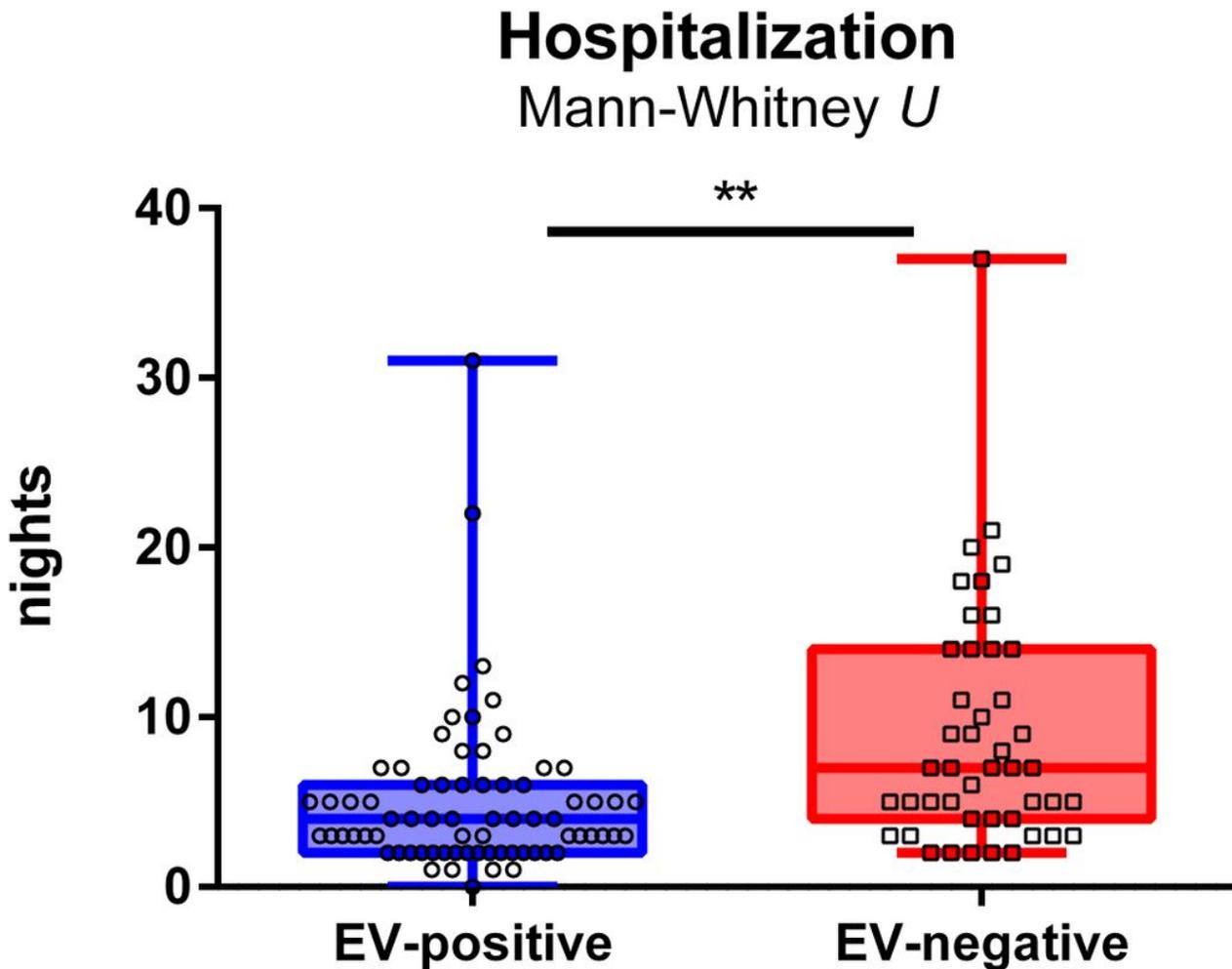


Figure 3

Hospitalization analysis of enterovirus (EV)-positive (n=72) and EV-negative patients (n=45).
Hospitalization of EV-negative patients is significantly longer ($p < 0.01$).