

1 **RESULTS OF A MULTINATIONAL STUDY SUGGESTS RAPID DIAGNOSIS AND**
 2 **EARLY ONSET OF ANTIVIRAL TREATMENT IN HERPETIC**
 3 **MENINGOENCEPHALITIS**

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107 **ABSTRACT**

108 Data regarding factors predicting unfavorable outcomes in adult herpetic meningoencephalitis
109 (HME) cases is scarce in the literature. We conducted a multicenter study to provide insights
110 into the predictors of outcome with special emphasis to use and timing of antivirals. Overall,
111 501 patients with molecular confirmation from the cerebrospinal fluid were included from 35
112 referral centers in 10 countries. Overall, 438 patients were found to be eligible for the
113 analysis. Finally, 232 (52.9%) patients experienced unfavorable outcomes; 44 died and 188
114 survived with sequelae. Age (OR 1.04, 95% CIs 1.02-1.05), Glasgow coma scale (OR 0.84,
115 95% CIs 0.77-0.93), symptomatic period of 2-7 days (OR 1.80, 95% CIs 1.16-2.79) and over
116 seven days (OR 3.75, 95% CIs 1.72-8.15) until treatment commenced, predicted unfavorable
117 outcomes. The outcome in HME patients is related to a combination of therapeutic and host
118 factors. This study suggests that rapid diagnosis and early administration of antiviral
119 treatment in HME patients are keys to favorable outcome.

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122 INTRODUCTION

123 Encephalitis due to Herpes Simplex Virus (HSV) is the most frequent form of sporadic
124 fatal encephalitis in the world and accounts for 10-20% of all viral encephalitis worldwide (1-
125 3). The annual incidence for herpetic meningoencephalitis (HME) per 100.000 is around 0.2-
126 0.4 in adults (4). In addition, HME cases experience exceedingly high unfavorable outcomes
127 including death and long term sequelae despite treatment (5-8).

128 There were studies assessing the outcomes particularly by comparing the efficacies of
129 herpetic antiviral drugs in the past (9, 10). To the best of our knowledge, data assessing
130 thoroughly the predictors of unfavorable outcome in HME patients do not exist in the
131 literature. One more potential limitation of the studies published was that they included cases
132 without virological confirmation (11-13), thus blurring the inferences. Hence, in this
133 multinational study we included HME patients solely with definite virological diagnosis.
134 Consequently, our study makes use of the largest case series ever reported in the literature to
135 provide data for the predictors of unfavorable outcome in HME.

136 METHODS AND MATERIALS

137 Study design

138 This retrospective multicenter study included hospitalized patients from referral
139 centers in 10 countries (Croatia, Czech Republic, Denmark, Egypt, France, Iraq, Italy,
140 Lebanon, Slovenia, and Turkey) between 2000 and 2013. Only the adult patients with HME
141 over the age of 15 were included. No control groups were included for this study. Dr. Lütfi
142 Kirdar Training and Research Hospital's Review Board in Istanbul approved the study and
143 informed consent was exempt.

144 The inclusion criteria comprised the presence of all of the following:

145 1. Positive CSF-PCR result for HSV-1 or HSV-2 or both in a patient with
146 meningoencephalitis.

147 2. The unlikely presence of any other infectious disease of the brain.

148 **Definitions**

149 **Meningoencephalitis:** The clinical and/or radiological and/or laboratory presentation
150 compatible with encephalitis (3, 8, 14) and meningitis (1, 15). The clinical findings related to
151 encephalitis mainly included alterations in conscious, language and behavioral abnormalities,
152 memory impairment, and seizures. The magnetic resonance imaging and/or
153 electrophysiological studies and/or CSF analysis were used to provide clues of the
154 encephalitic component of the disease (3). Meningitis was identified by the presence of
155 abnormal number of leucocytes in the CSF along with compatible clinical findings like fever,
156 headache, meningism, cranial nerve palsies, or altered consciousness (16).

157 **Unfavorable outcome:** Patients who died of HME or survived with sequelae.

158 **New onset convulsion:** Convulsion observed between the onset of symptoms and the start of
159 antiviral treatment for HME.

160 **Immunosuppression:** If the patient was under a long-term steroid treatment or had diseases
161 causing immunosuppression such as malignancy, autoimmune disease or diabetes, she or he was
162 classified in this category.

163 **Motor symptoms:** Locomotor deficiency, paresis, tetraparesis, hemiparesis, quadriparesis,
164 quadriplegia, spasticity, left foot drop or disrupted motoric skills.

165 **Statistical analysis**

166 Statistics were done on the software package, Stata 13.1 (StataCorp Texas, USA). In
167 univariate analysis; categorical variables were compared by Pearson's chi-squared test and
168 where applicable by Fisher's exact test. Continuous variables were compared by Student's t-

169 test or by Wilcoxon rank-sum test depending on the normality assumption for which
170 Shapiro-Wilk and Shapiro-Francia tests were used.

171 A total of 3% (15/438) of observations were missing. Missingness pattern indicated
172 this as "missing completely at random". Therefore missing observations were not filled via a
173 multiple imputation procedure.

174 Binary logistic regression model was constructed via a bootstrap resampling procedure
175 described in details elsewhere (17). Briefly, data set was replaced by resampling 200 times
176 during logistic regression analysis of the full model consisting all potential variables.
177 Eventually, variables with frequencies exceeding 30% of bootstrapped datasets with 0.1
178 significance threshold were included in the final model. The final model was tested with
179 logistic regression including all possible interaction terms. Co-linearity was also tested and
180 eliminated.

181 RESULTS

182 In this study, 501 HME patients' data was submitted from 35 referral centers in 10
183 countries [Turkey (n=144), Denmark (n=127), France (n=64), Slovenia (n=54), Croatia
184 (n=32), Iraq (n=30), Czech Republic (n=23), Italy (n=12), Lebanon (n=8), Egypt (n=7)].
185 Sixty-three patients were excluded either due to missing critical data or for the absence of
186 molecular confirmation leaving 438 patients eligible for outcome analysis. HSV 1/2 PCR was
187 found to be positive in 105 patients. HSV-1 DNA was positive in 300 and HSV-2 DNA was
188 positive in 79 cases. A brain biopsy was not performed in any of the patients. In this study,
189 375 (85.6%) patients received intravenous aciclovir and in 53 (12.1%) cases oral valaciclovir
190 was given sequential to intravenous aciclovir treatment. Nine cases were treated with
191 valaciclovir. Finally, one case received intravenous ganciclovir sequential to intravenous
192 aciclovir. The mean treatment duration of aciclovir alone arm was 21.6 ± 12.3 days while

193 valaciclovir alone was given for a mean of 10.3 ± 4.6 days. In intravenous aciclovir followed
194 by oral valaciclovir group, the drugs were given 15.5 ± 10.7 and 32.7 ± 18.9 days respectively.
195 The mean dose of intravenous aciclovir was 36.7 ± 5.7 mg/kg/day. In this study, 232 (52.9%)
196 patients experienced unfavorable outcomes. Forty-four HME patients died and 188 survivors
197 of the disease have experienced sequelae at the end of antiviral treatment. Overall, there were
198 313 disorders attributed to HME in 188 patients with sequelae. Memory disorder (n=62),
199 behavioral disorders (n=55), speech impairment (n=53), motor symptoms (n=40), epilepsy
200 (n=34), cognitive impairment (n=29), headache (n=13), psychiatric disorders (n=10), balance
201 disorder (n=6), and visual disturbances (n=5) were the frequent reasons of unfavorable
202 outcome in descending order. Tinnitus, sleeping disorder, coma, autoimmune encephalitis,
203 neurogenic bladder, and autonomy loss were seen in single cases.

204 Baseline characteristics of the study group are presented in table 1. Briefly study group
205 consisted of patients with a mean age of 50.6 (± 18.3) years and 48.4% (212/438) was male
206 gender. Almost half of the patients (44.5%; 195/438) received anti-viral treatment during the
207 first two days after the onset of symptoms. The median of elapsed time between the onset of
208 symptoms and antiviral treatment was 3 days (IQR 1, 5). In this study, 10% (44/438) died
209 while 42.9% (188/438) survived with severe sequelae. Univariate comparison of variables
210 between patients with favorable and unfavorable outcomes is presented in table 2. Age, male
211 gender, longer time gap between onset of symptoms and anti-viral treatment, lower Glasgow
212 coma scale (GCS) scores and convulsion were significantly different in patients with
213 unfavorable outcomes. Among these, however, only age, GCS score, and time to antiviral
214 treatment were included in the final model (table 3).

215 This multivariate model found that delay in establishing an effective anti-viral
216 treatment significantly increases unfavorable outcome. Accordingly, delay of more than seven
217 days causes a significant increase of unfavorable outcome among patients.

218 This is documented by the multivariate model, where odds ratio for delay in onset of
219 aciclovir of more than seven days is 3.75 (95% CIs 1.72-8.15) and two to seven days is
220 1.80(95% CIs 1.16-2.79) are significant whereas odds ratio of less than or equal to two days is
221 0.48 (95% CI, 0.32-0.74; p-value, 0.001) is protective (estimates by univariate logistic
222 regression).

223 Predicted percentages of unfavorable outcome versus elapsed time since the onset of
224 symptoms are presented in figure 1, where unfavorable outcome increases from 0.44 to 0.71
225 depending on the delay in establishing an effective anti-viral treatment. Observed outcomes
226 against predicted outcomes estimated by the logistic were in perfect agreement (Figure 2).

227 The multivariate model documented that age and GCS independently predicts
228 unfavorable outcome. The relation between these and the outcome is shown in Figure 3.
229 Briefly unfavorable outcome is more frequent among older patients exceeding 80% among
230 geriatric patients. On the other hand an interaction between age and male gender was found
231 indicating that elderly males experience more unfavorable outcomes. Lower GCS scores were
232 found with more unfavorable outcome exceeding 80% in patients with scores lower than five.

233 DISCUSSION

234 There are a number of published reports with relatively small case series in the
235 literature assessing unfavorable outcome in HME. Advanced age (10, 18, 19), lower GCS
236 (10), extent of brain involvement (20, 21), low serum albumin level (18), duration of disease
237 (20), delayed aciclovir use (18, 19, 21-24), presence of red blood cells in CSF (19), and
238 immunosuppression (24) have been found to be associated with poorer outcomes in HME In
239 this study, we detected that a combination of therapeutic and host factors contributed to
240 outcomes in HME patients. Advancing age, delayed start of antivirals, and worsening of
241 conscious determined with GCS contributed to the development of unfavorable outcomes in

242 these patients. In a relatively large study by Raschilas, higher Simplified Acute Physiology
243 Score II and delay in initiation of antiviral therapy were associated with poor prognosis. These
244 results are quite in accordance with this study. On the other hand, the data related to the
245 efficacy of treatment in HSV-2 meningitis is rather unclear in the literature (25, 26). The host
246 parameters directly affect the course of central nervous system (CNS) infections. In different
247 types of CNS infections, age and lower GCS scores have long been known to have poor
248 outcomes (27-29). Our HME data were also in accordance with the other infectious CNS
249 disorders and with the initial reports of adult HME series (10, 18, 19). According to our
250 results, patients with GCS score of less than five experienced unfavorable outcome more
251 frequently. Added to that, older males were more likely to have unfavorable outcomes from
252 HME. On the other hand, convulsions are believed to occur in patients with poor outcomes
253 (30). In this study, we could not disclose a significant relation between new onset convulsions
254 and poor outcome in HME patients.

255 In daily medical practice the use of aciclovir in standard dosages has been reported to
256 be of paramount importance in HME patients (1, 3, 8). But, the optimum timing of aciclovir
257 administration has been unclear in improving outcomes. Added to that, the benefit of
258 empirical use of aciclovir in patients with a likely diagnosis of encephalitis, rather than those
259 with confirmed HSV encephalitis, has not been proven yet in a randomized controlled clinical
260 trial (1). In a study 17 out of 24 (71 %) of patients with suspected encephalitis did not receive
261 empirical aciclovir in the emergency department, but after inpatient admission (median time
262 16 hours; 95% CI, 7.5 to 44 hours). In this study, three of five confirmed HSV encephalitis
263 were not given aciclovir in the emergency department (31). On the other hand, in a large
264 study a mean delay of 5.5 ± 2.9 days elapsed between the onset of symptoms and initiation of
265 antiviral treatment (22). These data indicate that the early start of antiviral treatment is not
266 likely in HME patients. This study suggests that aciclovir administered within the first two

267 days after the onset of symptoms significantly contributed to better outcomes. The goal of
268 empirical antiviral treatment is to improve prognosis in patients who are ultimately proven to
269 have HME. Thus, suspected encephalitis patients should be urgently given antiviral treatment
270 when the results of diagnostic studies are pending.

271 Although it would be very difficult to provide such a large cohort prospectively, the
272 major limitation of this study is its' retrospective design. The discrimination of pure
273 meningitis and pure encephalitis was very difficult in a retrospective study since they have
274 been known to be two interrelated syndromes with quite a similar clinical presentation and
275 thus, we cautiously favored not to discriminate these two entities. On the other hand, the
276 major problem was the microbiological confirmation of HSV cases due to diagnostic
277 difficulties in previous studies (32, 33). Since PCR testing in the CSF has an overall
278 sensitivity and specificity of more than 95% in HME (8), we view the inclusion of only CSF
279 PCR positive cases to be a strength of the study. Added to that, the predicted and observed
280 probabilities of the final model were in perfect agreement in this study.

281 In conclusion, the outcome in HME patients is directly related to both therapeutic and
282 host factors. Host factors like age, gender, unconsciousness and seizures detected during
283 initial evaluation, and coexistent immunosuppressive conditions may not be preventable for
284 the treating clinician. However, the major concerns should be the both rapid diagnosis and the
285 early start of antiviral treatment either in suspected or proven HME cases.

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388 **FIGURE LEGENDS**

389 **Figure 1.** Predictions of anti-viral treatment timing for unfavorable outcome (mean, 95% CIs)

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391 **Figure 2.** Observed outcomes against predicted outcomes estimated by the model

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393 **Figure 3.** Predictive margins of “Age” and “Glasgow coma scale (mean, 95% CIs)

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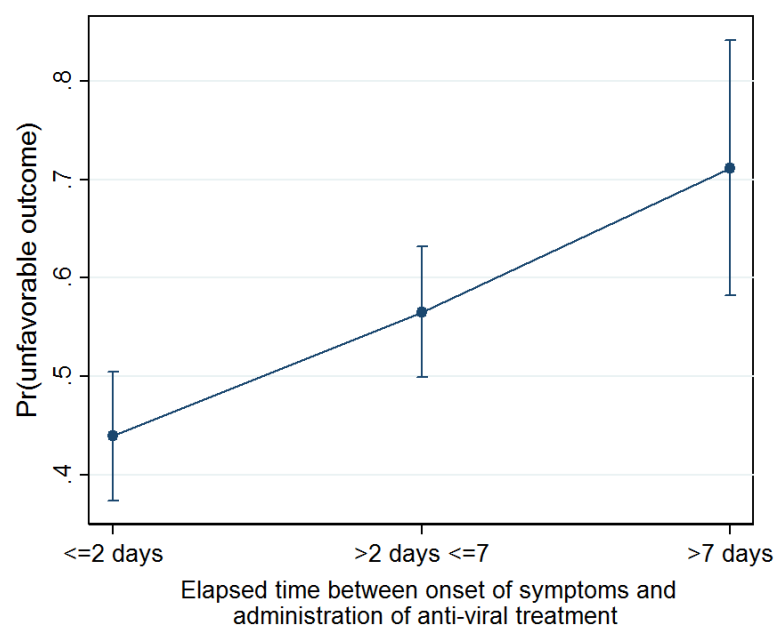


Figure 1. Predictive margins with 95% confidence intervals of “elapsed time between onset of symptoms and the start of anti-viral treatment” to unfavorable outcome

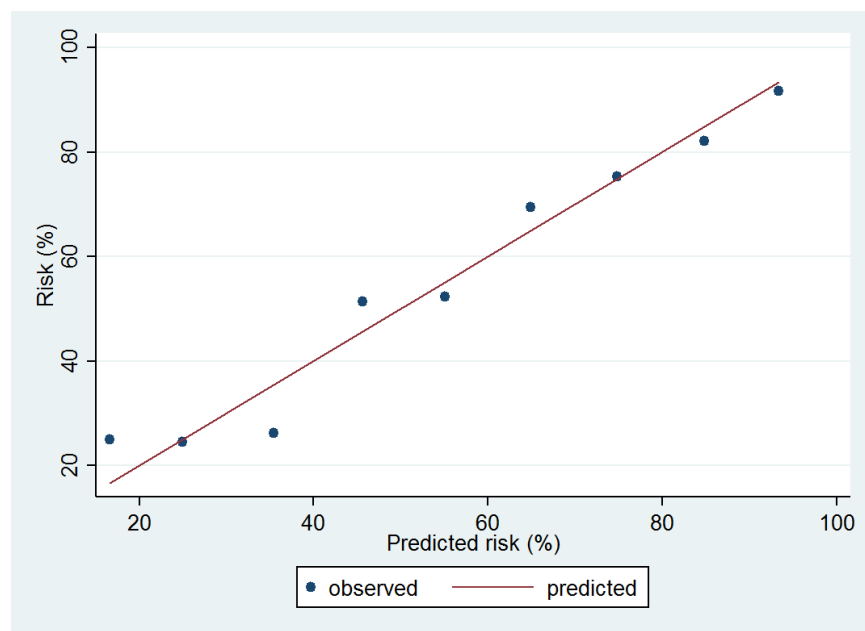


Figure 2. Observed outcomes against predicted outcomes estimated by the model

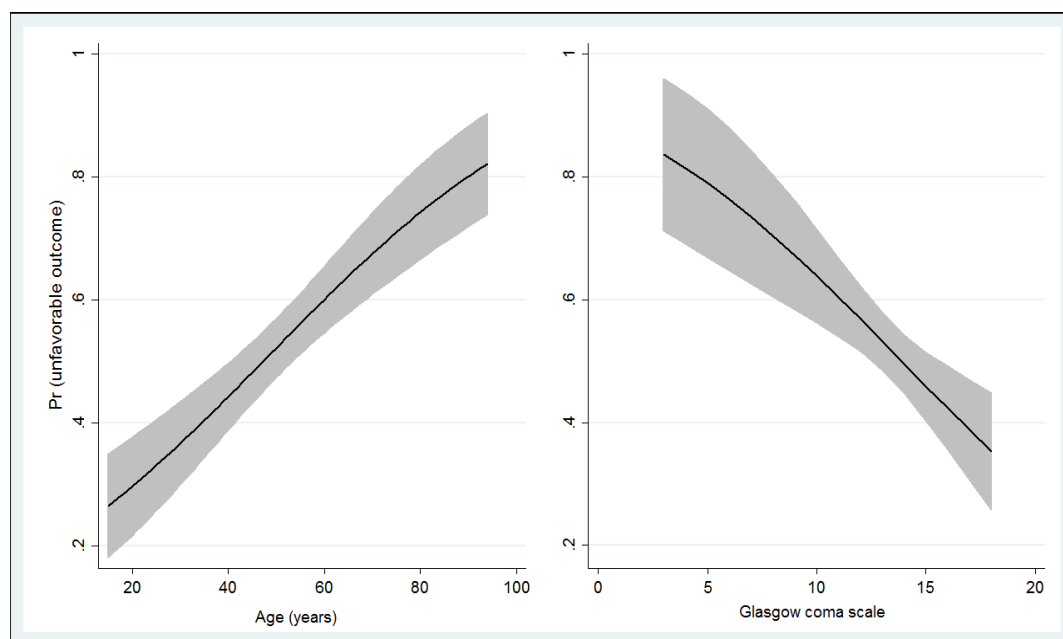


Figure 3. Predictive margins of “Age” and “Glasgow coma scale (mean, 95% CIs)

Table 1. Baseline characteristics

Variables	Value (n=438)
Age (years), mean +/- SD	50.58+/-18.27 ^a
Gender	
Women	226 (51.6%)
Man	212 (48.4%)
Elapsed time between OS & AVT ^b	
<=2 days	195 (44.5%)
2>days<=7	191 (43.6%)
>7 days	47 (10.7%)
Missing data	5 (1.1%)
Glasgow coma scale, median (IQR)	14 (13, 15)
New onset convulsion ^c	
No	343 (78.3%)
Yes	91 (20.8%)
Missing data	4 (0.9%)
Immunosuppression ^d	
No	379 (86.5%)
Yes	59 (13.5%)
Outcome	
Favorable	206 (47.0%)
Unfavorable	232 (53.0%)
Died	44 (10.0%)
Survived with severe sequel	188 (42.9%)

^a n=438^b Elapsed time between onset of symptoms and the start of anti-viral treatment^c Convulsion observed before therapy^d Long term steroid use or other immunosuppressive state

Table 2. Comparison of variables among patients with favorable and unfavorable outcomes

	Outcome		<i>p</i> -value
	Favorable (n=206)	Unfavorable (n=232)	
Age (years), mean +/- SD	44.50+/-16.80 ^a	55.97+/-17.86	<0.001
Gender			0.005
Women	121 (58.7%)	105 (45.3%)	
Man	85 (41.3%)	127 (54.7%)	
Elapsed time between OS & AVT ^b			<0.001
<=2 days	113 (55.7%)	82 (35.7%)	
>2 days <=7	78 (38.4%)	113 (49.1%)	
>7 days	12 (5.9%)	35 (15.2%)	
Glasgow coma scale, mean+/-SD	13.80+/-2.15 ^c	12.57+/-3.05	<0.001
New onset convulsion ^c	31 (15.1%)	60 (26.2%)	0.005
Immunosuppression ^d	24(11.7%)	35(15.1%)	0.29

^a n=206 vs n=232 for favorable and unfavorable outcome patients respectively^b Elapsed time between onset of symptoms and administration of anti-viral treatment^c Convulsion observed before hospital admission^d Long term steroid use or other immunosuppressive state

Table 3. Final model including independent predictors of unfavorable outcome

	OR ^a	95% CIs		<i>p</i>
		Low	High	
Age (years)	1.04	1.02	1.05	0.000
Glasgow coma scale	0.84	0.77	0.93	0.000
Elapsed time ^b				
>2 days ≤7 days	1.80	1.16	2.79	0.009
>7 days	3.75	1.72	8.15	0.001

^a OR, odds ratio^b Elapsed time between onset of symptoms and administration of anti-viral treatment