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Persistent headaches one year after bacterial meningitis: prevalence, determinants and impact on quality of life

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Abstract

Background.

Little is known on headaches long-term persistence after bacterial meningitis and on their impact on patients' quality of life.

Methods.

In an ancillary study of the French national prospective cohort of community-acquired bacterial meningitis in adults (COMBAT) conducted between February 2013 and July 2015, we collected self-reported headaches before, at onset, and 12 months (M12) after meningitis. Determinants of persistent headache (PH) at M12, their association with M12 quality of life (SF 12), depression (Center for Epidemiologic Studies Depression Scale) and neuro-functional disability were analysed.

Results.

Among the 277 alive patients at M12 87/274 (31.8%), 213/271 (78.6%) and 86/277 (31.0%) reported headaches before, at the onset, and at M12, respectively. In multivariate analysis, female sex (OR: 2.75 [1.54–4.90]; $p < 0.001$), pre-existing headaches before meningitis (OR: 2.38 [1.32–4.30]; $p < 0.01$), higher neutrophilic polynuclei percentage in the CSF of the initial lumbar puncture (OR: 1.02 [1.00-1.04]; $p < 0.05$), and brain abscess during the initial hospitalisation (OR: 8.32 [1.97–35.16]; $p < 0.01$) were associated with M12 persistent headaches. Neither the responsible microorganism, nor the corticoids use were associated with M12 persistent headaches. M12 neuro-functional disability (altered Glasgow Outcome Scale; $p < 0.01$), M12 physical handicap (altered modified Rankin score; $p < 0.001$), M12 depressive symptoms ($p < 0.0001$), and M12 altered physical ($p < 0.05$) and mental ($p < 0.0001$) qualities of life were associated with M12 headaches.

Conclusion.

Persistent headaches are frequent one year after meningitis and are associated with quality of life alteration.

Introduction

Community-acquired bacterial meningitis (CABM) is a rare but very severe event. It occurs in 1 to 2 per 100 000 inhabitants in occidental countries each year [1,2], and its mortality rate is approximately 17% [2,3]. Long-term complications such as cognitive impairment, motor sequelae, seizures and hearing loss are also described, and guidelines suggest to perform a neurological clinical examination before and one month after discharge in adults and children [4–7]. Hearing tests during the first hospitalization and every

3 months in children are also mandatory [8]. Recent data on long-term patients' assessment are limited, particularly in adults, and factors associated with long-term neurological or sensory outcomes are not well defined [5,9].

We recently performed a large, multicentric, prospective cohort study assessing the in-hospital and one-year outcomes after CABM [3]. We found that the impact was significant in terms of handicap and quality of life one year after the meningitis episode. Persistent headaches seemed to be very frequent in surviving patients and to highly contribute to this negative impact on quality of life but were not specifically analysed during this first study.

Post-meningitis headaches are well defined in the international classification of headache disorders upgraded in 2018 (ICHD-3) by the international headache society, as headaches persisting more than 3 months after a meningitis episode [10]. However, little is known about their epidemiology and determinants. Identifying preventable factors associated with the occurrence of persistent headaches (PHs) following CABM could be of great interest if headaches contribute to the lower quality of life experienced by patients one year after meningitis.

Thus, we analysed data from the French cohort to specifically study post-meningitis-related persistent headaches one year after CABM. The incidence, risk factors and potential impact on quality of life were assessed.

Methods

Study design

The French prospective cohort COMBAT is a multicentre prospective cohort involving 69 hospitals in France designed to assess the epidemiology of CABM and has been described in detail elsewhere [3]. In brief, adult patients (≥ 18 years) with a confirmed diagnosis of CABM were included between February 2013 and July 2015. Epidemiological, clinical, biological, microbiological and therapeutic data were prospectively recorded at admission, during the in-hospital period, at discharge and at 12 months. The presence of pre-existing headaches before CABM was also recorded. Month 12 data were obtained using a standardized questionnaire during a specific consultation by telephone contact (with the patient, a relative or the general practitioner if the patient could not answer himself) or with the help of a paper questionnaire sent by mail if the patient was not able to answer by phone. The presence of headaches at 12 months and their intensity and frequency were systematically recorded. Patients were divided into two groups: patients with headaches at 12 months (PHs group) and patients without headaches (NH group, for No Headache). Among the PHs group, we identified the patient with or without pre-existing headaches. Other collected data were vital status, disability, general condition, neurological condition, depressive symptoms, hearing loss and health-related quality of life.

Headache definitions and neurological assessment at 12 months

Patients were considered to experience PHs if they reported any persistent pain or uncomfortable sensation of the head at month 12. Patients were asked about the intensity of headaches, dichotomized with the value reported on a numerical scale (from 0 to 10) as mild (1–3), moderate (4–6), severe (7–10), and the frequency of headaches (dichotomized as occasional or regular).

At discharge of meningitis hospitalisation and at month 12, neuro-functional disability was assessed by the Rankin-modified score as follows: 0 = absence of disability, 1 = low disability, 2 = mild disability, 3 = moderate disability, 4 = moderately severe disability, 5 = major disability, 6 = death [11]. At month 12, the following data were also assessed: Glasgow Outcome Scale (GOS) (1 = death, 2 = vegetative state, 3 = severe handicap, 4 = moderate handicap, 5 = good recovery) [12]; Depressive symptoms using the Center for Epidemiologic Studies Depression (CES-D) scale, with a threshold of 23 for women and 17 for men [13,14]; Quality of life using the SF12 score, with two composite scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) HRQL scores; these scores range from 0 to 100, with a high value indicating good HRQL (health-related quality of life) [15,16].

Statistics

First, a descriptive analysis was performed on the entire cohort of surviving patients with available data at 12 months. Categorical variables were summarized as counts (percentage), and frequency distributions were compared between PHs group and NH group with Chi-square test or Fisher's exact test as appropriate. Continuous variables were expressed as the median [IQR], and differences were tested between PHs group and NH group with the independent t-test for normally distributed variables or the Mann-Whitney U test otherwise.

Second, we analysed factors at the time of meningitis associated with persistent headaches at 12 months among following variables: the patient's background characteristics, initial clinical presentation, biological results at inclusion, causative microorganisms and the initial treatments. All variables with a p-value < 0.20 in the bivariate analysis were entered into a multivariate logistic regression model with a backward variables selection approach and a significance level at 5%. We performed these analyses in the entire cohort and then in the population of patients who did not report pre-existing headaches.

Finally, we analysed in bivariate analysis the association between persistent headaches at 12 months and concomitant M 12 Glasgow Outcome Scale, depressive symptoms, and quality of life. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc, Cary, NC).

Ethics and regulatory issues

The COMBAT study was registered with ClinicalTrials.gov (NCT02916732) and received ethics approval by the Comité de Protection des Personnes Ile de France CPP 4 (IRB 00003835) (2012-16NI) and the CNIL (commission nationale de l'informatique et des libertés) (EGY/FLR/AR128794).

Results

Patient characteristics

Among the 533 patients included in COMBAT study, 443 were alive at discharge and 439 at M12 [3]. Among these 439 patients, 284 (64.7%) answered the questionnaire at 12 months and 277 gave information about headaches and were thus included in the analysis (Fig. 1). Pre-existing headaches were reported in 87/274 (31.8%); headaches were reported at hospital admission of CABM in 213/271 (78.6%) of patients. The most frequent responsible microorganism was *Streptococcus pneumonia* (47.7%). Most of the patients were treated with a 3rd generation cephalosporin (271/274 (98.9%)), and 199/274 (72.6%) received steroids as adjunctive treatment (Table 1).

Table 1

Comparison between patients with and without headaches at 12 months: determinants of headaches among baseline characteristics

Patients' characteristics	Entire population (N = 277, unless specified [/n])	Patients with headaches at 12 months (N = 86, unless specified [/n])	Patients without headaches at 12 months (N = 191, unless specified [/n])	P value (bivariate analysis)
Baseline characteristics and demography				
Age (years)	56.2 [37.3–65.8]	54.2 [34.8–61.4]	58.3 [38.3–66.8]	0.2041
Sex				
Female	132 (47.7)	54 (62.8)	78 (40.8)	0.0007
F/M ratio	0,91	1,69	0,69	
Preexisting headaches	87/274 (31.8)	39/85 (45.9)	48/189 (25.4)	0.0008
Intensity of headaches:				0.2573
→ Mild (0, 1, 2, 3)	35 (40.2)	19 (48.7)	16 (33.3)	
→ Moderate (4, 5, 6)	27 (31.0)	9 (23.1)	18 (37.5)	
→ Severe (7, 8, 9, 10)	25 (28.7)	11 (28.2)	14 (29.2)	
Initial presentation				
Acute headaches at diagnosis	213/271 (78.6)	73/84 (86.9)	140/187 (74.9)	0.0254
Microbiological documentation (LP, blood cultures, biopsy)				0.4346
<i>Streptococcus pneumoniae</i>	127/266 (47.7)	35/82 (42.7)	92/184 (50.0)	
<i>Neisseria meningitides</i>	70/266 (26.3)	23/82 (28.0)	47/184 (25.5)	
<i>Listeria monocytogenes</i>	11/266 (4.1)	3/82 (3.7)	8/184 (4.3)	
<i>others*</i>	58/266 (21,8)	21/82 (25,6)	37/184 (20,1)	
CSF characteristics :				

Patients' characteristics	Entire population (N = 277, unless specified [/n])	Patients with headaches at 12months (N = 86, unless specified [/n])	Patients without headaches at 12monts (N = 191, unless specified [/n])	P value (bivariate analysis)
- White cells' count (/mm3)	2200.0 [605.0-5800.0] (/268)	3100.0 [865.0-7400.0]	1781.0 [436.0-4180.0] (/182)	0.0094
- Percentage of neutrophils	94.0 [85.0–97.0] (/260)	95.0 [90.0–98.0] (/84)	92.0 [83.5–96.0] (/176)	0.0108
- Proteins level (g/L)	4.1 [2.0-6.2] (/265)	4.5 [2.3–6.7] (/85)	4.1 [1.7–6.1] (/180)	0.2218
- Glucose level (mmol/L)	0.7 [0.1–2.5] (/257)	0.3 [0.1–2.2] (/83)	0.9 [0.1–2.7] (/174)	0.2655
Biology in blood samples:				
- CRP rate (mg/L)	182.0 [90.0-291.0] (/230)	179.0 [87.0-301.0] (/78)	191.5 [90.5-285.5] (/152)	0.8473
- White blood cells' count (/mm3)	15060 [9900.0-20740] (/266)	14800 [9570.0-21030] (/85)	15190 [10400–20300] (/181)	0.6268
- Percentage of neutrophils	89.2 [85.0-92.8] (/240)	89.4 [85.7–93.2] (/79)	89.0 [85.0–92.0] (/161)	0.3805
Initial care and treatments				
Time interval between admission and the first lumbar puncture:				0.8790
- < 1 day	194/274 (70.8)	62 (72.1)	132/188 (70.2)	
- 1 day	61/274 (22.3)	19 (22.1)	42/188 (22.3)	
- >= 2days	19/274 (6.9)	5 (5.8)	14/188 (7.4)	
Time interval between admission and first dose of antibiotics:				0.9662

Patients' characteristics	Entire population (N = 277, unless specified [/n])	Patients with headaches at 12months (N = 86, unless specified [/n])	Patients without headaches at 12monts (N = 191, unless specified [/n])	P value (bivariate analysis)
- < 1 day	204/275 (74.2)	63 (73.3)	141/189 (74.6)	
- 1 day	61/275 (22.2)	20 (23.3)	41/189 (21.7)	
- >/= 2 days	10/275 (3.6)	3 (3.5)	7/189 (3.7)	
Corticoids** use:	199/274 (72.6)	64 (74.4)	135/188 (71.8)	0.8158
Clinical course				
Complications during treatment	237 (85.6)	71 (82.6)	166 (86.9)	0.3403
Seizure	27/275 (9.8)	10 (11.6)	17/189 (9.0)	0.4963
Ventriculitis	24/275 (8.7)	10 (11.6)	14/189 (7.4)	0.2503
Altered mental status (including coma)	38/275 (13.8)	13 (15.1)	25/189 (13.2)	0.6739
Brain abscess	12/275 (4.4)	7 (8.1)	5/189 (2.6)	0.0542
Stroke (probable and confirmed)	101 (36.5)	30 (34.9)	71 (37.2)	0.7142
Septic shock	38/273 (13.9)	10 (11.6)	28/187 (15.0)	0.4582
More than one lumbar puncture performed during the clinical course	57 (20.6)	22 (25.6)	35 (18.3)	0.1669
Modified Rankin disability score at discharge:				
Any symptom or handicap (1 to 5)	153/264 (58.0)	48/83 (57.8)	105/181 (58.0)	0.9781

Note: Data are median [IQR] or n/N (%)

* *Haemophilus* spp. (including *H.influenzae*), *Streptococcus* spp. (non-pneumococcus), *Escherichia coli*, *Staphylococcus aureus*, *Mycobacterium tuberculosis complex* and others

** dexamethasone was used in 98% of cases (10mg*4 per day (every 6 hours), during 4 days)

Denominators correspond to patients for who data were obtained at baseline and at 12 months

At 12 months, 86/277 (31.0%) patients reported persistent headaches, of whom 46/85 (54.1%) patients had no pre-existing headache before meningitis. No difference was documented in terms of M12 headache frequency and intensity between the patients with or without pre-existing headaches. Forty-eight patients of 87 who reported pre-existing headaches declared no longer suffering from headaches at M12.

Determinants on the entire cohort at twelve months

Bivariate analyses

The results of the bivariate analyses are presented in Table 1. Headaches were more likely to occur in women than in men (62.8% of women in PHs group vs 40.8% in NH group, $p < 0.001$) and in patients who experienced pre-existing headaches (45.9% vs 25.4%, $p < 0.001$) or acute headaches at meningitis onset (86.9% vs 74.9%, $p < 0.05$). The white blood cell level in the CSF of the initial lumbar puncture was higher in the PHs group than in the NH group (3 100/mm³ [IQR 865-7 400] vs. 1 781 [IQR 436-4 180], $p < 0.01$). No association was found between M12 headaches and the meningitis causative microorganism, antibiotics used, corticosteroid used, and the time interval between hospital admission and antibiotic initiation. Among the different meningitis-related complications, only brain abscesses tended to be statistically associated with a higher probability of 12-month headaches, documented in 8.1% and 2.6% in the PHs and NH groups, respectively ($p < 0.01$).

Multivariate analysis

In the multivariate analysis, female sex (OR 2.75 [1.54–4.90], $p < 0.001$), pre-existing headaches (OR 2.38 [1.32–4.30], $p < 0.01$), brain abscess (OR 8.32 [1.97–35.16], $p < 0.01$) and a higher percentage of neutrophils polynuclear in the CSF of the initial lumbar puncture (OR 1.02 [1.00-1.04], $p < 0.05$) were significantly associated with persistent headaches at 12 months (Table 2). Analyses performed in the population of patients without pre-existing headaches (187 patients) showed similar results, with a younger age as a complementary determinant of persistent headaches in multivariate analysis (age (years); OR 0.98 [0.96–0.998]).

Table 2
Factors associated with headaches in the multivariate analysis

Number of patients: N = 248 (79 with headaches at 12M - 169 without headaches)	OR (95% IC)	p-value	OR	p-value N = 255 (83 with H ; 172 without H)
Women vs men	2.79 [1.52–5.13]	0.0010	2.75 [1.54–4.90]	0.0006
Antidepressant drugs use before meningitis	1.08 [0.38–3.07]	0.8836		
Pre-existing headaches	2.36 [1.26–4.45]	0.0077	2.38 [1.32–4.30]	0.0041
Acute headaches at meningitis diagnosis	1.59 [0.71–3.59]	0.2608		
Brain abscess	8.99 [2.06–39.35]	0.0035	8.32 [1.97–35.16]	0.004
Absence of DIVC	3.30 [0.35–31.11]	0.2974		
More than 1 lumbar puncture performed	1.52 [0.76–3.06]	0.2404		
Number of white cells in initial LP (/mm ³) for an increasing of 1000/mm ³	1.00 [0.98–1.01]	0.7348		
% of neutrophils in initial LP	1.02 [0.997–1.04]	0.0939	1.02 [1.00–1.04]	0.0391
Note: Variables included in the model: sex, antidepressant use before meningitis, headaches before meningitis, acute headaches at diagnosis, brain abscess, DIVC, total number of lumbar punctures, number of white blood cells in CSF in initial lumbar puncture, neutrophils percentage in CSF in initial lumbar puncture				

Association between M12 headaches and concomitant patient characteristics

The presence of headaches at 12 months was significantly associated with an altered M12 neurological condition: the Glasgow Outcome Scale was more often altered (36.1% of patients with a score < 5 in the PH group vs 20.9% in the NH group, $p < 0.01$; Table 3). The modified Rankin Disability Score was also altered in the PHs group as compared to the NH group (57.1% of patients experiencing any handicap vs

34.6% (p < 0.001)) while it was not different between the groups at hospital discharge (any symptom or handicap for 48/83 (57.8%) in the PHs group vs 105/181 (58.0%) in the NH group, p = 0.9781, Table 1).

Table 3
Impact of persistent headaches on neurological status

12 months' assessment	Entire population (N = 277, unless specified, [/n])	Patients with headaches at 12 months (N = 86, unless specified, [/n])	Patients without headaches at 12 months (N = 191, unless specified, [/n])	P value (bivariate analysis)
Return to work	112/265 (42.3)	36 (44.4)	76/184 (41.3)	0.6336
Anxiolytic or hypnotic drugs use	31 (11.2)	14 (16.3)	17 (8.9)	0.0715
Antidepressant drugs use	23 (8.3)	10 (11.6)	13 (6.8)	0.1784
Deafness (HHIE-Screening > = 9)	73/273 (26.7)	27/85 (31.8)	46/188 (24.5)	0.2072
GOS *				0.0079
5 (good recovery)	201/270 (74.4)	53/83 (63.9)	148/187 (79.1)	
< 5 (any neurological handicap)	69/270 (25.6)	30/83 (36.1)	39/187 (20.9)	
Modified Rankin disability score **				0.0005
0 (no symptom)	161/275 (58.5)	36/84 (42.9)	125 (65.4)	
1 to 5 (any symptom or handicap)	114/275 (41.5)	48/84 (57.1)	66 (34.6)	
Depressive symptoms ***	86/264 (32.6)	41/83 (49.4)	45/181 (24.9)	< 0.0001
SF-12 score (physical) ****	49.0 [39.8–54.3] (/265)	45.1 [37.0–52.8] (/82)	51.3 [42.0–54.8] (/183)	0.0126
SF-12 score (mental) ****	50.8 [40.9–55.8] (/265)	45.7 [35.9–51.8] (/82)	53.1 [42.7–56.8] (/183)	< 0.0001

Note: Data are median [IQR] or n/N (%); Denominators correspond to patients for who data were obtained at baseline and at 12 months

* GOS =Glasgow Outcome Scale : 2=vegetative state, 3=severe handicap, 4=moderate handicap, 5=good recovery

** Modified Rankin disability score: 0= absence of disability, 1=low disability, 2=mild disability, 3=moderate disability, 4=moderately severe disability, 5=major disability, 6=death.

*** CES-D score: ≥ 23 for women / ≥ 17 for men

**** SF-12: the calculation of the scores is such that a higher score corresponds to a better health. "Two composite scores can be derived from the SF-12 Health Survey: a Physical Component Summary (PCS) and a Mental Component Summary (MCS) HRQL score. These scores range from 0 to 100, with a high value indicating good HRQL. An individual was defined as having a "normal" physical (or mental) HRQL if his PCS (or MCS) was higher than the 25th percentile of the distribution of the score in the general French population of the same age group and gender, using an existing approach to clinically interpret the results
»

At M 12, depressive symptoms were also more frequent in the PHs group (49.4%) than in the NH group (24.9%, $p < 0.0001$). The quality of life was significantly poorer in the PH group than in the NH group for the physical component summary (PCS) (median scores of 45.1 [IQR 37.0-52.8] and 51.3 [IQR 42.0-54.8], respectively, $p < 0.02$) and for the mental component summary (MCS) (median scores of 45.7 [IQR 35.9–51.8] and 53.1 [IQR 42.7–56.8], respectively, $p < 0.0001$).

Discussion

Our study provides interesting information regarding persistent headaches (PHs) 12 months after bacterial meningitis in adult patients : i) PHs are frequent, observed in 31% of patients in general and in 25% of patients who did not report pre-existing chronic headaches before meningitis; ii) female sex, pre-existing headaches, a high percentage of polynuclear neutrophils in the initial CSF, and the occurrence of a brain abscess during the clinical course of meningitis are associated with 12-month PHs; iii) PHs probably play a detrimental role in the quality of life of patients, since the patients experiencing PHs demonstrated worse HRQL SF-12 scores than patients without PHs.

The prevalence of PHs after CABM is not well known thus far. Only retrospective studies published before 2000 have addressed this point, finding that 31% [17] to 46% [18] of patients experience PHs after CABM. We found similar results, with almost one-third of patients suffering from PHs one year after a bacterial meningitis event. This is higher than the proportion of patients with PHs following other acute nontraumatic neurological events, as only 12% of patients experience PHs three years after ischemic or hemorrhagic stroke [19] and 25% after cervical artery dissection [20]. However, since headaches are frequently reported in the general population [10], [21], we tried to better characterize the responsibility of

CABM for PHs in evaluating the frequency of incident PHs, noticed by patients without pre-existing headaches. Incident PHs were frequent and reported by 25% of these patients. We also investigated whether CABM could worsen headaches in patients with pre-existing headaches, but no differences in headache intensity or frequency before and after meningitis were noticed. Surprisingly, we found that a significant proportion of patients with pre-existing headaches (48/87) declared no longer presenting headaches 12 months after the event. One hypothesis is that CNS infectious episodes could influence the psychopathology of patients suffering from previous headaches and could modify the patient's perception of their headaches after this event.

Unfortunately, we did not find any amendable factor associated with PHs. The risk of PHs was lowered neither by a prompter diagnosis nor by optimal management of the CABM. Indeed, the time elapsed between admission and the first lumbar puncture did not influence the risk. This risk was also not lowered by rapid administration of the first dose of antibiotics. We found that PHs were more frequent among patients with pre-existing headaches and among females. These results are in line with the results of a previous study; Bohr *et al.* [17] found that women suffered more often from headaches than men after meningitis but without a clear explanation of this result. A high percentage of neutrophils in the initial CSF analysis was associated with a higher risk of PHs in our multivariate analysis. This could suggest a possible role of inflammation in headache genesis. Of note, corticosteroids use initiated after CSF analysis was not associated with a reduction of headache rate at month 12. Finally, the presence of brain abscess was strongly associated with PHs. Only very few patients experienced this complication, and we were therefore not able to demonstrate whether a specific management of brain abscess, e.g., surgical drainage, could lower the risk of PHs.

Bacterial meningitis is known to be associated with possible long-term cognitive impairments, mental retardation in childhood, deafness, and sleep disorders [2,4–7,22–25] but not with PHs. Therefore, PHs can be a neglected symptom during classical patient follow-up after CABM. However, in our study, PHs were highly associated with an impaired quality of life 12 months after bacterial meningitis. We found a strong association between PHs and neurological disabilities, with worse GOS and Rankin scores in the PH group than in the NH group. There were also more patients with depressive symptoms in the PH group, although association does not mean causal relationship. However, in line with previous studies [26,27], we think that PHs can have a detrimental role in mental and physical status, leading to depressive symptoms and, therefore, inducing an impaired quality of life.

Our study has several limitations. First, the questionnaire was not designed to specifically describe 12-month headaches. However, thanks to a prospective, systematic and codified interview at 12 months performed by a well-trained evaluator, we were able to obtain reliable data about headaches. Second, no amendable factors associated with PHs were documented in our study. Thus, we are unable to propose changes to the initial care of CABM that could lower the risk of PHs. Third, we were not able to describe the type of headaches declared by the patients and to characterize them as headaches migraines, cluster headaches or new daily persistent headaches. Only a prospective study focused on this topic could address this point.

Conclusion

Headaches persisting 12 months after a bacterial meningitis episode are frequent, with a potential impact on patients' quality of life. Such as rarely described in the literature, they seem to be an underestimated sequela. Similar to deafness and neurological sequelae, PHs must be systematically tracked during the follow-up of patients after CABM. A better understanding of their pathophysiology is needed to avoid them, detect them as early as possible, assist suffering patients and finally improve patients' quality of life.

Declarations

COMBAT STUDY GROUP

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Figures

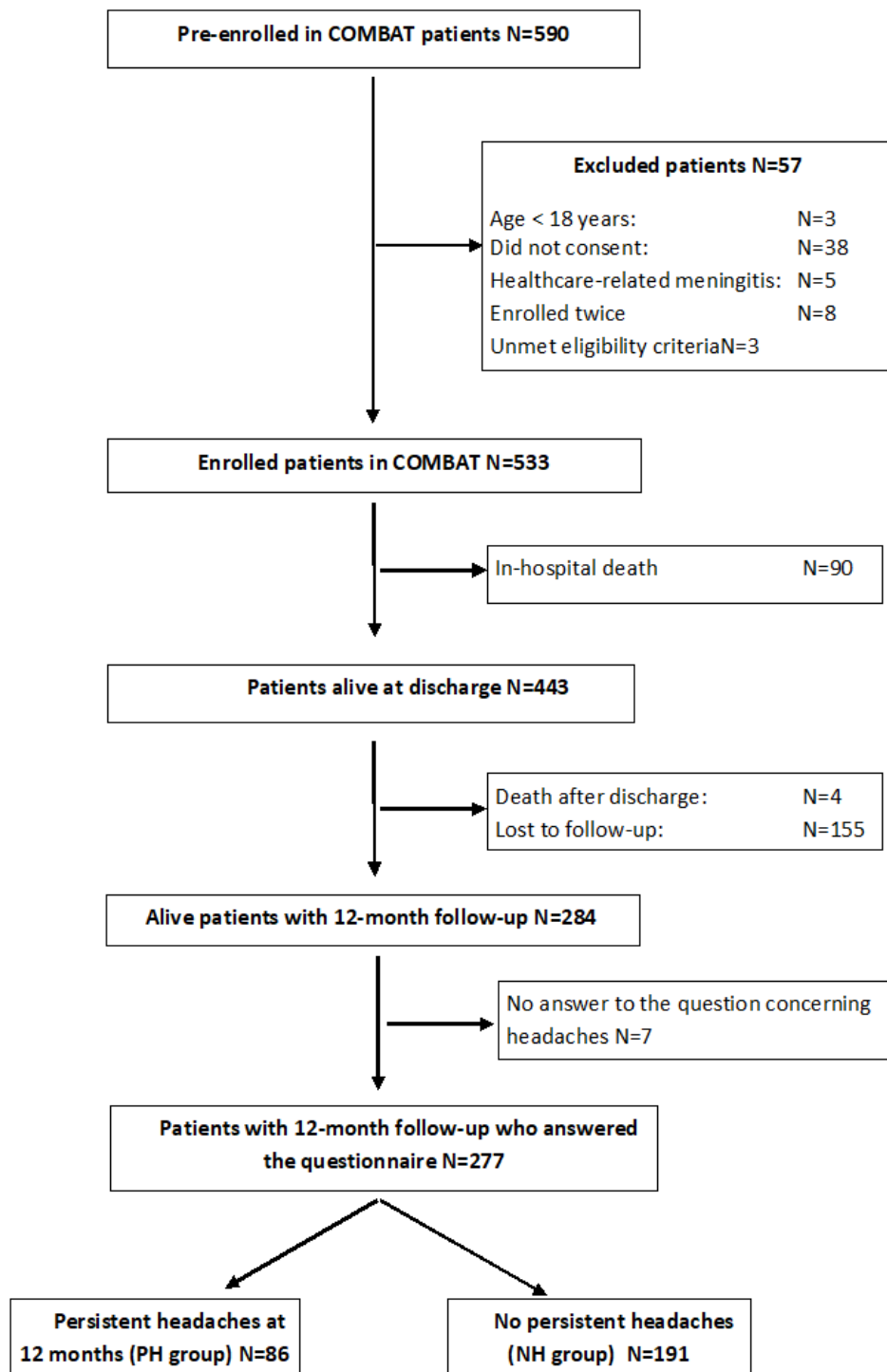


Figure 1

Flow chart