Prevalence of Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review and Meta-analysis

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Abstract

Background

As a common complication after aneurysmal subarachnoid hemorrhage, the prevalence of pituitary dysfunction ranges widely at the global level and has not been synthesized by meta-analysis for a few years. Updated estimates of the prevalence of pituitary dysfunction after aneurysmal subarachnoid hemorrhage are urgently needed to improve recognition and attention from medical.

Methods

We comprehensively searched four literature databases including Scopus, Embase, Web of Science and PubMed, and performed a random-effects meta-analysis for the search results. Heterogeneity in the prevalence estimates was analyzed by subgroup analysis in terms of WHO region and type of pituitary dysfunction.

Results

27 studies with 1848 subjects were included in this study. The pooled prevalence of pituitary dysfunction in the acute phase was 49.6% (95% CI, 32.4%-66.8%), and decreased in the chronic phase to 30.4% (95% CI, 21.4%-39.4%). Among the hormonal deficiencies, growth hormone dysfunction was the most prevalent in the acute phase with 36.0% (95% CI, 21.0%-51.0%), and in the chronic phase was hypoadrenalism accounting for 21.0% (95% CI, 12.0%-29.0%). While referring to the WHO region, the prevalence of pituitary dysfunction in the acute phase was the highest in SEARO, up to 81.0% (95%CI, 77.0%-86.0%), while the EURO with the highest prevalence of pituitary dysfunction in the chronic phase, was only 33.0% (95%CI, 24.0%-43.0%). Moreover, single pituitary hormone dysfunction occurred more frequently than that of multiple regardless of in the acute or chronic phase.

Conclusions

In up to 49.6%, patients with aneurysmal subarachnoid hemorrhage may be complicated with pituitary dysfunction, which deserved more attention. Although the prevalence decreased over time, early detection and early treatment were more beneficial for the quality of life of patients. However, the number of existing studies on PD after aSAH is limited. Therefore, more studies based on larger populations and countries are necessary to provide early warning.

1 Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a type of hemorrhagic stroke, specifically referring to SAH caused by aneurysm rupture[1]. Globally, the average annual incidence of aSAH in the population is 6 to 10 per 100 000 individuals[2], and the average mortality rate is up to 35%[3]. But profitting from the gradual progress of medical technology, approximately 30% of patients still can survive and resume independent living[4]. Moreover, on account of the mean age of onset of aSAH is 50 years old, with the highest incidence in 40–60 years old[5–9], the age is a period of major responsibility for family and society and active creation of social value. Therefore, the prognosis of this group of patients is particularly important.

In recent years, increasing survivors of aSAH have found emerging symptoms such as cognitive impairment, memory deterioration, fatigue, sexual dysfunction, and loss of weight after treatment[5–15]. These symptoms were later confirmed to be caused by pituitary dysfunction (PD), which was labeled as a common complication after aSAH[6, 10, 13, 16]. PD after aSAH seriously affected the quality of life and social function of patients and made patients suffer from the disease in long term[17]. Thus, more and more studies have focused on the prevalence, early identification, and prevention of PD after aSAH with good neurological recovery[18]. However, studies on the prevalence of PD after aSAH are only based on a few small cohorts, and the studies on the acute and chronic phases of PD are scattered[19–23]. Therefore, a comprehensive statistical analysis of the prevalence of PD after aSAH is meaningful for early diagnosis, early warning and treatment of PD.

All we know, a systematic review and meta-analysis reported a pooled prevalence of PD in the acute phase after aSAH of 49.3%, which decreased in the chronic phase being 25.6%[24]. While another meta-analysis reported that the prevalence of PD after aSAH was 31% in the acute phase and 25% in the chronic phase[25]. These two studies have been published more than five years ago, and new related studies have emerged during this period, so it is necessary to update the results. Additionally, these studies did not focus on the prevalence of individual pituitary hormone dysfunction, such as adrenocorticotropic hormone dysfunction, gonadotropin dysfunction, and thyroid-stimulating hormone dysfunction. Because of different treatments for different hormonal disorders, targeted guidance cannot be provided without the prevalence of each pituitary hormone dysfunction.

Hence, the aim of this systematic review is to update and analyze all current literature on PD in patients with aSAH and to identify the following items. First, the prevalence of acute and chronic phases of PD after aSAH will be calculated, whether diagnosed by basal hormonal or stimulation experiments. Then, the prevalence of various types of PD in the acute and chronic stages will be counted up separately, including adrenocorticotropic hormone (ACTH) deficiency, growth hormone deficiency (GHD), thyroid-stimulating (TSH) hormone deficiency, gonadotropin (Gn) deficiency, etc. Lastly, the prevalence of PD in each WHO Regional Office and the prevalence of single/multiple pituitary hormone dysfunctions will be analyzed.

2 Methods

2.1 Literature search

In order to expand the search range, we adopted the strategy of medical subject heading (MeSH) terms combined with text words for retrieval and performed up to May 2022 using Scopus, Embase, Web of Science, and PubMed. At the same time, relevant studies were manually retrieved for the supplement. The search strategy of each database is detailed in Supplementary Table 1. All retrieved documents were imported into Endnote X9 (Thomas Reuters 2019) to facilitate subsequent literature screening.

2.2 Inclusion and exclusion criteria

Studies included in this meta-analysis should meet the following conditions: (1) the criteria for the diagnosis of aSAH need to be stated in the text, which was confirmed by CT scan and digital subtraction angiography (DSA), or the location distribution of all aneurysms was explained in the article. (2) articles should include the diagnostic criteria and incidence of at least one of the following diseases: PD, GHD, ACTH deficiency, TSH deficiency, Gn deficiency, hyperprolactinemia and diabetes insipidus. (3) patients without endocrine dysfunction before aSAH. (4) patients who are >18 years old. (5) only English-language studies can be incorporated into this study.

If the type of article were reviews, letters, case reports, conference abstracts and commentaries et al. or articles for which the original text was not available, they would be excluded. Furthermore, duplicate publications of the included studies were not available and articles in which the prevalence of disease was not given or cannot be calculated were also excluded.

2.3 Study selection

Titles or abstracts of publications suspected of meeting the eligibility criteria for this systematic review were selected for detailed review. Then two authors will carefully review the full text and appendix apart. Inclusion was required after consensus between the two authors. In cases of disagreement after consultation between the two authors, review was performed by the third author, and inclusion was permitted after agreement.

2.4 Quality assessment

We used the Joanna Briggs Institute Prevalence Critical Appraisal Tool[26] to assess the study quality of the articles that met full-text inclusion criteria. This tool includes ten questions answered with Yes, No, Unclear, and Not/Applicable. All studies were assessed by two authors (A and B) independently and checked by the third author (author C) to resolve any disagreements.

2.5 Data extraction

Two authors jointly produced data extraction form first. According to this form, the data of included articles was manually extracted and cross-checked by two authors (A and B) separately. When multiple articles describing the same case series were published and the data in them was consistent, we used the latest article. If not, given the presence of recall bias, we used the earliest published articles. We preferentially adopted the incidence rate measured by the stimulation test[27], and if not, we chose the incidence rate measured by the basal hormone test[8]. Disagreements to extracted data were resolved by consensus or by a third author (author C).

2.5.1 Study characteristics

We extracted the author of the article, year of publication, country, sample size, gender ratio, age, study design, World Federation of Neurological Surgeons Scale grade, Glasgow Coma Scale score, Hunt and Hess Scale grade, Fisher grade or modified Fisher grade, location of the aneurysm, treatment of aneurysm, and duration of follow-up of the subjects. Then the countries of the individual study populations were classified according to the World Health Organization regional office[28], and the location of the aneurysm was categorized as an anterior circulation aneurysm and a posterior circulation aneurysm.

2.5.2 Outcome measures

Primary outcomes in this study were the prevalence of PD in the acute and chronic phases (the acute phase refers to the occurrence of pituitary dysfunction within the first 6 months after aSAH, and the chronic phase is vice versa[18]), while the prevalence of each hormone deficiencies, i.e., deficiency of ACTH, GH, TSH, Gn, prolactin, cortisol, testosterone, were regarded as the secondary outcomes.

In each included article, the prevalence of PD and each hormone deficiency after aSAH was calculated by dividing the number of patients with a certain hormonal deficiency by the total of subjects receiving the corresponding hormone testing experiment at the same point. Considering the loss or death of patients during follow-up, we used the actual number of follow-up patients as the denominator when calculating the frequency of pituitary dysfunction and each hormone deficiency in the subsequent follow-up. If the number of follow-up cases was not reported, we used the original number of cases at enrollment as the denominator for the calculation of prevalence rates at follow-up, regardless of the loss of population follow-up.

2.6 Statistical Analysis

All studies were stratified by the acute and chronic phases of PD. Subsequently, two groups in each stratification were identified according to the cut-off points: 3 months and 1year. The global pooled prevalence of PD with inverse-variance weights obtained from random-effect meta-analysis models was computed utilizing the metaprop command in Stata, showing a prevalence and 95% CIs. Heterogeneity was assessed using the I^2 statistic, which ranged from 0–100%, with I^2 >50% required for subgroup analyses. Finally, the source of heterogeneity in two sets of primary outcomes, i.e., the prevalence of PD, was estimated by subgroup analysis in terms of WHO Regional Office (ARFO, PAHO, SEARO, EURO, EMRO, WPRO) and single/multiple pituitary hormone deficiencies. All statistical analyses were performed using Stata (version 16.0; StataCorp).

3 Results

3.1 Search results

A total of 10395 records (8653 in Scopus, 753 in Embase, 704 in Web of Science, 284 in PubMed and 1 from manually retrieved) were identified through an initial systematic search, of which 1369 articles were removed due to duplicated citations. Then the remaining 9026 articles were reviewed by abstracts and titles. According to our inclusion and exclusion criteria, we adopt 109 articles progressing to the full-text review stage. By reviewing the full-text literature, 82 studies were excluded for the reasons shown in Fig. 1. Finally, 27 studies were included in the final meta-analysis. The process of the systematic literature search is displayed in a flow diagram in Fig. 1.

3.2 Study characteristics

The included studies were published from 2004 and 2022, and the number of patients ranged from 20 to 417 per study, with a total of 1848 individuals. According to the zoning of the WHO Regional Office, a total of 21 of these studies have focused on EURO[8, 10, 13, 14, 19, 21–23, 29–41], the remaining 3 on SEARO[42–44], 2 on PAHO[45, 46], and 1 on WPRO[47]. Of these studies, 22 articles had prospective study designs, and 5 were cross-sectional studies. Excluding studies that the location of aneurysms could not be acquired, a total of 740 individuals had anterior circulation aneurysms, 146 were located in the posterior circulation, and 24 were mixed types. All relevant information for the included studies is detailed in Table 1.

Table 1
Characteristics of the studies included in the analysis NR: not reported

Author (year)	Sample size, n (M/F)	Country	WHO Regional Office	Age (mean or median)	Design	WFNS (mean or median)	GCS (mean or median)	Hunt & Hess (mean or median)	Fisher (median)	Aneurysm location	
										Anterior circulation	Poster circula
Aimaretti 2004 [29]	40 (14/26)	Italy	EURO	51.0 ± 2.1	prospective	NR	NR	NR	NR	NR	NR
Dimopoulou 2004 [10]	30 (14/16)	Greece	EURO	50 ± 13	prospective	NR	NR	2	2	24	6
Kreitschmann 2004 [13]	40 (14/26)	Germany	EURO	43.8 ± 7.6	cross sectional	NR	NR	2	3	26	8
Aimaretti 2005 [23]	32 (12/20)	Italy	EURO	51.9 ± 2.2	prospective	NR	NR	NR	2	NR	NR
Tanriverdi 2007 [19]	22 (11/11)	Turkey/Spain	EURO	47·9 ± 3·3	prospective	NR	NR	2	2	NR	NR
Klose 2010 [21]	62 (14/48)	Denmark	EURO	49	cross sectional	NR	NR	2	3	53	9
Jovanovic 2010 [38]	93 (30/63)	Serbia	EURO	48.0 ± 1.1	cross sectional	NR	NR	NR	NR	84	9
Lammert 2011 [39]	26 (6/20)	Germany	EURO	49.3	prospective	NR	NR	2	3	NR	NR
Schneider 2011 [8]	417 (139/278)	Germany	EURO	50.2 ± 11.6	cross sectional	NR	NR	2	NR	NR	NR
Lammert 2012 [40]	24 (4/20)	Germany	EURO	49.5 ± 14.5	prospective	NR	NR	2	3	NR	NR
Dutta 2012 [44]	60 (37/23)	India	SEARO	44.9 ± 13.1	prospective and retrospective	NR	NR	NR	NR	60	0
Lanterna 2013 [22]	26	Italy	EURO	53.5 ± 13.1	prospective	NR	NR	2	2	13	NR
Blijdorp 2013 [30]	43 (15/28)	Netherlands	EURO	56.6 ± 11.7	prospective	2	NR	NR	NR	24	19
Pereira 2013 [46]	66 (22/44)	Brazil	PAHO	48.3 ± 13.8	prospective	NR	13.8 ± 2.5	2	3	NR	NR
Karaca 2013 [33]	20 (12/8)	Turkey/Spain	EURO	47.6 ± 13	prospective	NR	NR	2	2	NR	NR
Khursheed 2013 [42]	73 (37/36)	India	SEARO	56 ± 13.5	prospective	3	NR	NR	3	NR	NR
Kronvall 2014 [14]	51 (8/43)	Sweden	EURO	55	prospective	NR	NR	2	3	NR	NR
Hannon 2015 [37]	100 (39/61)	Ireland	EURO	53	prospective	NR	NR	2	3	NR	NR
Tölli 2015 [41]	46(8/38)	Sweden	EURO	58.3 ± 10.5	prospective	NR	7.4 ± 3.9	4	4	36	11
Khajeh 2015 [36]	84 (28/56)	Netherlands	EURO	55.8 ± 11.9	prospective	2	13	NR	NR	49	35
Kronvall 2016 [35]	51 (8/43)	Sweden	EURO	55	prospective	NR	NR	NR	NR	NR	NR
Goto 2016 [47]	59 (19/40)	Japan	WPRO	58.0 ± 13.5	prospective	2	NR	3	NR	48	8 (both
Vieira 2016 [45]	92 (33/59)	Brazil	PAHO	48.5	prospective	1	15	2	3	83	9
Tölli 2017 [32]	35 (8/27)	Sweden	EURO	57.4 ± 9.9	prospective	NR	7.9 ± 4.2	3	4	28	6 (both
Giritharan 2017 [31]	100 (32/68)	UK	EURO	57 ± 10	cross sectional	1	NR	NR	4	72	10 (bo 18)

Author (year)	Sample size, n (M/F)	Country	WHO Regional Office	Age (mean or median)	Design	WFNS (mean or median)	GCS (mean or median)	Hunt & Hess (mean or median)	Fisher (median)	Aneurysm location	
										Anterior circulation	Poster circula
Jaiswal 2017 [43]	100 (38/62)	India	SEARO	43.6	prospective	NR	NR	NR	NR	95	5
Robba 2022 [34]	56 (14/42)	Italy/ Russia	EURO	56.3 ± 11.0	prospective	2.0 ± 1.6	11.6 ± 4.0	2.0 ± 1.4	NR	45	11

3.3 Quality assessment

The quality of most studies was judged to be moderate. Participants, being able to represent the aSAH population, were recruited from Neurosurgical centers of large hospitals or Tertiary care centers. Most studies provided detailed inclusion and exclusion criteria, allowing the results of the present study to be representative of this population. Sample sizes were adequate in 3 studies (12%), but it is understandable that the rest of the studies fail to recruit enough individuals considering the low prevalence of aSAH (6 to 10 per 100 000 individuals). Full quality assessment was shown in Table 2.

Table 2
Quality assessment of included studies

Author(years)	1.Was the sample representative of the target population?	2.Were study participants recruited in an appropriate way?	3.Was the sample size adequate?	4.Were the study subjects and the setting described in detail?	5.Was the data analysis conducted with sufficient coverage of the identified sample?	6.Were objective, standard criteria used for the measurement of the condition?	7.Was the condition measured reliably?	8.Was there appropriate statistical analysis?	9.Are all important confounding factors/subgroups/ identified and acco
Aimaretti 2004	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	No
Dimopoulou 2004	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Kreitschmann-andermahr 2004	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Aimaretti 2005	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	No
Tanriverdi 2007	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	No
Klose 2010	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No
Jovanovic 2010	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Schneider 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Lammert 2011	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Lammert 2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Dutta 2012	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Pereira 2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Blijdorp 2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Karaca 2013	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	No
Khursheed 2013	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Lanterna 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kronvall 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Tolli 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Hannon 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Khajeh 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Goto 2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kronvall 2016	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	No
Vieira 2016	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Giritharan 2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Jaiswal 2017	Yes	Yes	No	Unclear	Unclear	Unclear	Unclear	Unclear	No
Tolli 2017	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Robba 2022	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No

3.4 Outcome measures

3.4.1 Pooled prevalence of PD in the acute and chronic phases after aSAH

Data from 14 literatures[8, 14, 19, 21, 22, 29, 34–36, 39, 42, 43, 45, 46] assessed the PD after aSAH in the acute phase (Fig. 2). The prevalence of PD after aSAH within 6 months was 0.50, which was estimated to vary from 0.32 to 0.67 (I^2 = 98.0%, P value <0.001), with a total of 1148 individuals. The subtotal prevalence of PD was 0.59 (95% CI, 0.44–0.75, I^2 = 95.9%, P value <0.001) within 3 months and 0.23 (95% CI, 0.13–0.33, I^2 = 75.6%, P value = 0.006) in 3–6 months. As shown in Fig. 2, it can be seen that the 95% confidence interval of the prevalence within 3 months and 3–6 months has no overlap, so the prevalence of PD within 3 months is significantly higher than that within 3–6 months (P value<0.001).

Similarly, 20 literatures' data[8, 10, 13, 19, 21, 23, 30, 31, 33–40, 42, 44, 45, 47] with a total of 1453 subjects evaluated PD after aSAH in the chronic phase (Fig. 3). The prevalence of PD after aSAH later than 6 months was 0.30, which estimated ranged from 0.21 to 0.39 (I^2 = 94.7%, P value <0.001). The subtotal prevalence of PD was 0.29 (95% CI, 0.12–0.46, I^2 = 97.5%, P value <0.001) during 6–12 months. When assessed after 12 months, the subtotal prevalence of PD was 0.31 (95% CI, 0.22–0.41, I^2 = 86.5%, P value <0.001). We found the prevalence rates of PD increased over time after 6 months but were not statistically significant (P = 0.817), indicating that the increase in prevalence was not very obvious.

3.4.2 Global analysis for PD

By comprehensive analysis of the literature we included, we calculated the prevalence of each hormone deficiency in the acute and chronic phases.

In the acute phase, 15 studies[14, 19, 21, 22, 29, 32, 34–36, 39, 41, 43, 45, 46] with a total of 739 participants evaluated the prevalence of ACTH deficiency which was 0.15 (95% CI, 0.09–0.21, I^2 = 90.0%, P value <0.001). The prevalence of GHD was 0.36 (95% CI, 0.21–0.51, I^2 = 94.6%, P value <0.001) which evaluated by 12 studies[14, 19, 21, 29, 34–36, 39, 43, 45, 46] with a total of 632 participants. A total of 786 participants from 15 studies[14, 19, 21, 29, 32, 34–36, 39, 41–43, 45, 46] assessed the prevalence of TSH deficiency that was 0.17 (95% CI, 0.09–0.24, I^2 = 94.7%, P value <0.001). Of 13 studies[14, 19, 21, 29, 34–36, 39, 42, 43, 45, 46] with a total of 705 participants evaluated the prevalence of Gn deficiency that was 0.33 (95% CI, 0.21–0.44, I^2 = 93.4%, P value <0.001). About hyperprolactinemia, the prevalence was 0.12 (95% CI, 0.07–0.16, I^2 = 69.3%, P value = 0.001) calculated by 12 studies[14, 19, 21, 29, 34, 35, 39, 42, 43, 45, 46] with a total of 621 participants. As shown in Table 3, it can be seen that the 95% confidence intervals of the prevalence of GHD or Gn deficiency and the remaining ACTH deficiency or hyperprolactinemia have no overlap respectively, so the prevalences of GHD or Gn deficiency were significantly higher than that of ACTH deficiency and hyperprolactinemia.

Table 3
Global Analysis and Subgroup Analysis of Pituitary Dysfunction in the acute phases CI: confidence interval, NA: not applicable.

Variable	No. of Articles	No. of Cases	No. of Participants	Prevalence (95% CI)	Heterogeneity		Sensitivity analysis	Subgroup difference
					Q test	I^2, %		
Global Analysis for classification of PD								
ACTH deficiency	15	121	739	0.15 (0.09, 0.21)	*P*<0.001	90.03%		NA
GH deficiency	12	215	632	0.36 (0.21, 0.51)	*P*<0.001	94.57%		NA
TSH deficiency	15	124	786	0.17 (0.09, 0.24)	*P*<0.001	94.66%		NA
Gn deficiency	13	238	705	0.33 (0.21, 0.44)	*P*<0.001	93.37%		NA
Hyperprolactinemia	12	64	621	0.12 (0.07, 0.16)	*P* = 0.001	69.28%		NA
Subgroup analysis of PD								
WHO region								*P*<0.001
ARFO	none	none	none	none	none	none		
PAHO	2	79	148	0.54 (0.46, 0.62)	NA	NA		
SEARO	2	115	173	0.81 (0.77, 0.86)	NA	NA		
EURO	11	301	827	0.47 (0.28, 0.65)	*P*<0.001	97.07%		
EMRO	none	none	none	none	none	none		
WPRO	none	none	none	none	none	none		
Type								*P* = 0.674
Single	11	175	606	0.28 (0.20, 0.35)	*P*<0.001	78.55%		
Multiple	11	175	606	0.25 (0.12, 0.37)	*P*<0.001	95.04%		

In the chronic phase, the prevalence of ACTH deficiency was 0.21 (95% CI, 0.12–0.29, I^2 = 91.21%, P value <0.001) which evaluated by 19 studies[10, 13, 19, 21, 23, 31–33, 35–40, 45, 47] with a total of 880 participants. Of 22 studies[10, 13, 19, 21, 23, 30–40, 44, 45, 47] with a total of 1018 participants evaluated the prevalence of GHD that was 0.18 (95% CI, 0.14–0.22, I^2 = 63.40%, P value <0.001). About TSH deficiency, the prevalence was 0.05 (95% CI, 0.02%-0.07%, I^2 = 41.94%, P value = 0.070) calculated by 22 studies[10, 13, 19, 21, 23, 31–40, 42, 44, 45, 47] with a total of 1062 participants. Of 22 studies[10, 13, 19, 21, 23,

31–40, 42, 44, 45, 47] with a total of 1062 participants evaluated the prevalence of Gn deficiency that was 0.14 (95% CI, 0.09–0.19, I^2 = 82.57%, P value <0.001). 19 studies[13, 19, 21, 23, 31–35, 37–40, 42, 44, 45, 47] assessed hyperprolactinemia after 6 months. This represents data from 918 participants, and the prevalence was 0.03 (95% CI, 0.01–0.04, I^2 = 0.00%, P value = 0.481). Among these hormone deficiencies, the 95% confidence intervals of the prevalence of ACTH deficiency or GHD or Gn deficiency and the remaining TSH deficiency or hyperprolactinemia have no overlap apart, which can be considered that the prevalences of the three hormone deficiencies were higher than that of TSH deficiency or hyperprolactinemia (Table 4). The amount of literature on diabetes insipidus was too small, so no further analysis was performed after statistics.

Table 4
Global Analysis and Subgroup Analysis of Pituitary Dysfunction in the chronic phases

Variable	No. of Articles	No. of Cases	No. of Participants	Prevalence (95% CI)	Heterogeneity		Sensitivity analysis	Subgroup difference
					Q test	I^2, %		
Global Analysis for classification of PD								
ACTH deficiency	19	124	880	0.21 (0.12, 0.29)	*P*<0.001	91.21%		NA
GH deficiency	22	180	1018	0.18 (0.14, 0.22)	*P*<0.001	63.40%		NA
TSH deficiency	22	33	1062	0.05 (0.02, 0.07)	*P* = 0.070	41.94%		NA
Gn deficiency	22	106	1062	0.14 (0.09, 0.19)	*P*<0.001	82.57%		NA
Hyperprolactinemia	19	22	918	0.03 (0.01, 0.04)	*P* = 0.481	0.00%		NA
Subgroup analysis of PD								
WHO region								*P*<0.001
ARFO	none	none	none	none	none	none		
PAHO	1	17	68	0.25 (0.15, 0.37)	NA	NA		
SEARO	2	21	133	0.05 (0.02, 0.09)	NA	NA		
EURO	18	396	1219	0.33 (0.24, 0.43)	*P*<0.001	93.12%		
EMRO	none	none	none	none	none	none		
WPRO	1	5	33	0.15 (0.05, 0.32)	NA	NA		
Type								*P*<0.001
Single	18	223	892	0.24 (0.16, 0.31)	*P*<0.001	90.73%		
Multiple	18	55	892	0.07 (0.05, 0.10)	*P* = 0.062	43.19%		

CI: confidence interval, NA: not applicable.

3.4.3 Subgroup analysis for PD

For the WHO Regional Office of PD after aSAH, the studies we included were located at EURO, SEARO, WPRO, and PAHO analyzing the prevalence of PD, respectively. Studies from the remaining two regions were not available.

Of the 15 studies, 11 studies[8, 14, 19, 21, 22, 29, 34–36, 39] with a total of 827 participants calculated the prevalence of PD to be 0.47 (95% CI, 0.28–0.65, I^2 = 97.07%, P value <0.001) in the EURO. For the rest of 4 studies, two studies[45, 46] from PAHO with a total of 148 participants had a calculated prevalence of 0.54 (95% CI, 0.46–0.62), and the other two studies[42, 43] from SEARO had a calculated incidence of 0.81 (95% CI, 0.77–0.86) with a total of 173 participants. We found statistical significance among three regions (Table 3, P values<0.001) about the prevalence of PD in the acute phase (Table 3).

Of the 22 studies, 18 studies[8, 10, 13, 19, 21, 23, 30, 31, 33–40] with a total of 1219 participants calculated the prevalence of PD to be 0.33 (95% CI, 0.24–0.43, I^2 = 93.12%, P value <0.0001) in the EURO. For the rest of 4 studies, two studies[42, 44] from SEARO with a total of 133 participants had a calculated prevalence of 0.05 (95% CI, 0.02–0.09), and one study[45] from PAHO had a calculated incidence of 0.25 (95% CI, 0.15–0.37) with a total of 68 participants, and the other one study[47] from WPRO had a calculated incidence of 0.15 (95% CI, 0.05–0.32) with a total of 33 participants. We found statistical significance among four regions (Table 4, P values<0.001) about the prevalence of PD in the chronic phase (Table 4).

In the acute phase, the random effects pooled meta-analysis performed on 11 studies with a total of 1212 participants showed an overall prevalence of single pituitary hormone dysfunction[14, 19, 29, 34–36, 39, 43, 45, 46] of 0.28 (95% CI, 0.20–0.35, I^2 = 78.55%, P value<0.0001) and an overall prevalence of multiple pituitary hormone dysfunctions[14, 19, 29, 34–36, 39, 43, 45, 46] of 0.25 (95% CI, 0.12–0.37, I^2 = 95.04%, P value<0.0001), respectively. As shown in Table 3, it can be seen that the prevalence of single pituitary hormone dysfunction was higher than that of multiple pituitary hormone dysfunction, but not statistically significant.

In the chronic phase, the random effects pooled meta-analysis performed on 18 studies with a total of 1784 participants showed an overall prevalence of single pituitary hormone dysfunction[10, 13, 23, 30, 31, 33–40, 42, 45, 47] of 0.24 (95% CI, 0.16–0.31, I^2 = 90.73%, P value<0.0001) and an overall prevalence of multiple pituitary hormone dysfunction[10, 13, 23, 30, 31, 33–40, 42, 45, 47] of 0.07 (95% CI, 0.05–0.10, I^2 = 43.19%, P value = 0.062), respectively. As shown in Table 4, it can be seen that the 95% confidence interval of the prevalence of single pituitary hormone dysfunction and multiple pituitary hormone dysfunctions has no overlap, so the prevalence of single pituitary hormone dysfunction is significantly higher than that of multiple pituitary hormone dysfunctions.

4 Discussion

Our meta-analysis demonstrates that the prevalence of PD after aSAH in acute phases decreased over time and tended to be stable in the chronic phases, which was consistent with previous studies[6]. To be specific, the prevalence of PD within 3 months in our meta-analysis was relatively high, up to 59.3%, which was the first pooled prevalence to the best of our knowledge. As Can et al.[25] indicated, endocrine changes, which were temporary and reversible, in the early stages of aSAH (within 3 months) can interfere with the assessment of PD. This may have contributed to the inflated prevalence of PD. Then affected by the prevalence of PD 3 months after aSAH, the overall prevalence in acute phases was high at 49.6%, which is similar to the results of Robba et al.[24], who reported a prevalence rate of 49.3% in PD after aSAH patients in the acute phase. Getting rid of prevalence within 3 months, the prevalence rate of 22.7% in PD between 3–6 months was comparable to that of PD in chronic phases (overall 30.4%, separate 28.9% and 31.2%) in spite of showing a slight increase over time without statistical significance. They were about the same as the study of Can et al.[25], showing the prevalence of 31% and 25% in PD from 3 to 6 months and later than 6 months after aSAH. From the above findings, we speculated that most patients complicated with PD between 3–6 months may last long, reminding us that this group of patients was the focus. Attention paid to patients with PD early in 3–6 months could advance the treatment for the disease and improve the quality of life for them in the long-term after aSAH. All in all, the results showed the improving or stable trend of PD with time, as other studies both analyzed the acute and chronic phases confirmed[20, 37, 42]. However, some authors[33, 40, 48] have reported that new hormone dysfunction may also occur during follow-up leading to a gradual increase in the prevalence of PD, which was also found in our study. The mechanism responsible for this difference needed to be further studied.

In the acute phase, a high prevalence of dysfunction has been seen in the growth hormone and gonadotropin, while the ACTH deficiency and GHD is more common in the chronic phase. This may be related to the particular vulnerability of these pituitary endocrine cells to various injuries[49]. In terms of the prevalence of hormonal dysfunction, Can et al[25]. reported a prevalence rate of 19.0% (95% CI, 13.0–26.0%) in GHD after aSAH patients in the chronic phase, and Dimopoulou et al.[10] reported a long-term prevalence rate of 13% in Gn deficiency and 7% in TSH deficiency, which were similar to our results. Additionally, we also found the prevalence of most hormonal disorders decreased over time, which further supported the decreasing prevalence of PD. However, a little needed to be notable that there was a slight increase in the prevalence of ACTH deficiency. But taking the 95% confidence intervals overlapped into consideration, the difference was not statistically significant and the above conclusion was still tenable. The mechanism of changes in these hormonal disorders is not clear, and may have to do with structural hypothalamic-pituitary damage and adaptive mechanisms to acute diseases[21, 50].

After the analysis of the WHO Regional Office where the included literature was located, we found that the prevalence of PD after aSAH in the acute phase was the highest in SEARO, which was significantly higher than that in EURO and PAHO. In the chronic phase, the prevalence of PD in the EURO is more common than in each region. Up to now, there were no previous studies on WHO Regional Office in PD after aSAH, thus our results about the prevalence of PD in each region could provide a reference for the detection and prevention of PD after aSAH in the corresponding WHO Regional Offices. Due to the advanced medical level of EURO, the result was exactly because of the sufficient number of studies. In view of the small number of studies in other regions, leading to the explanation of the conclusions was not convincing enough, so the number of studies needs to be further expanded.

Lastly, we found that single pituitary hormone dysfunction occurs a little more than three times than that multiple, which were similar to previous studies[24], but only in the chronic phase. In the acute phase, the prevalence of single hormone dysfunction was slightly higher than that of multiple, but not statistically significant.

Limitations

Several limitations of this study should be recognized. The criteria of diagnosis for PD after aSAH have not been unified, and the diagnostic methods are different in some studies. Thus, the large variation in the frequency of hormone deficiencies that we extracted from studies may be due to different methodological tools for assessing pituitary function. Moreover, the time to perform the diagnostic test also varied and not all patients adopted dynamic testing to assess which may lead to an underestimation of the number of PD patients.

5 Conclusion

In conclusion, our results showed that the prevalence of PD after aSAH decreased over time. Respectively, the prevalence of the acute phase and chronic phase was 0.50 and 0.30. Among the hormonal deficiencies, GHD was the most prevalent in the acute phases, and ACTH deficiency in the chronic phases. Given the heterogeneity in prevalence reported between various studies, it is recommended to further clarify the diagnostic methods in the future for more high-quality epidemiologic investigations. Some countries have limited research on PD after aSAH, and it is recommended to pay more attention to this disease within the Region of Americas, Eastern Mediterranean Region, Southeast Asia Region, and Western Pacific Region.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All information analyzed in this study was available from the corresponding author on reasonable request.

Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Authors' contributions

Baosheng Huang and Fan Meng conceptualized and designed the study, provided financial support, and make a final evaluation of argument about studies selection. Xiaowei Song and Shengnan Cong determined the retrieval formula, conducted studies selection and data extraction, carried out data processing and paper writing, drafted the initial manuscript, and reviewed and revised the manuscript. Ming Zhang and Xiaokui Zhang collected data, carried out the initial analyses, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

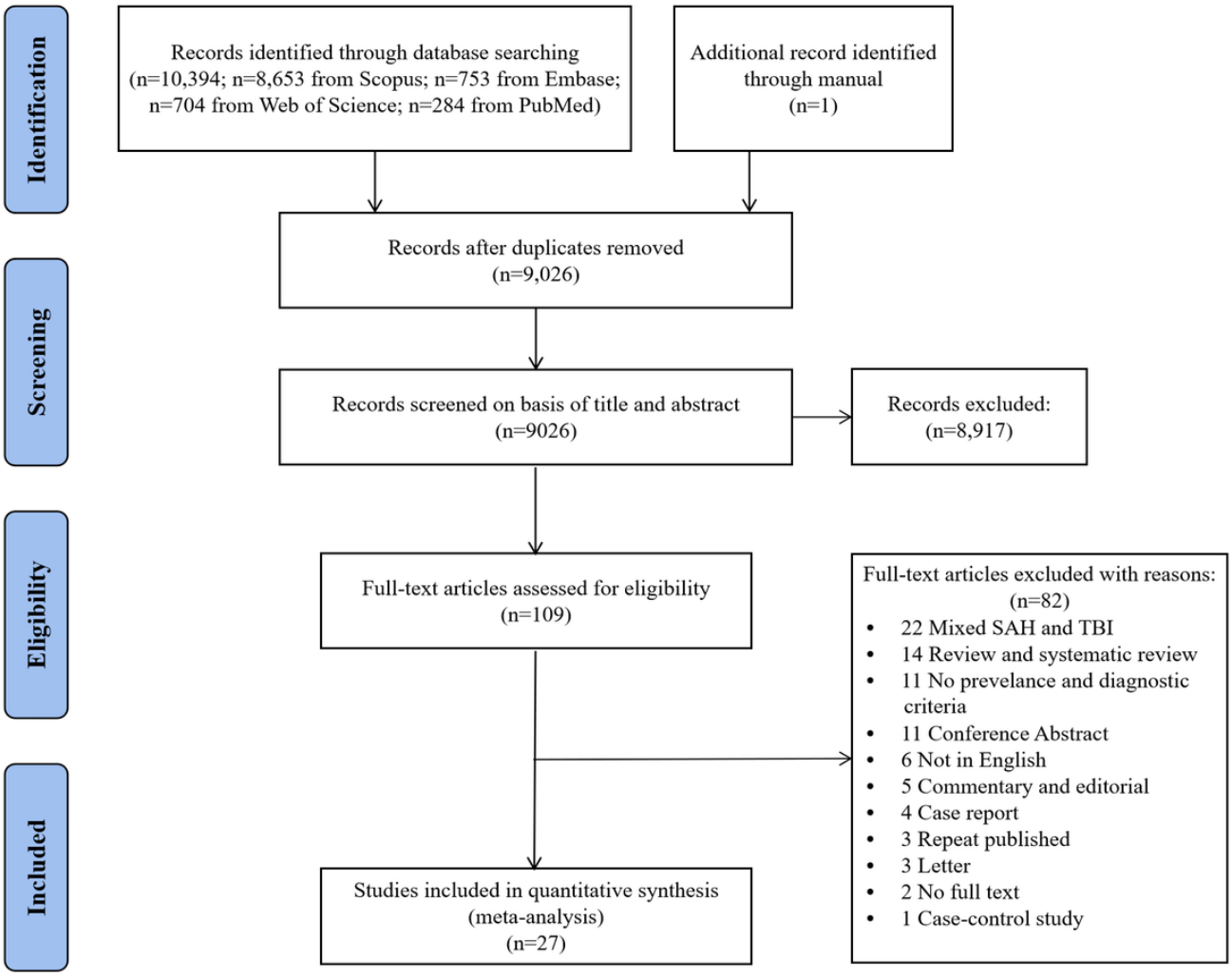

Figure 1

Flowchart of the search strategy.

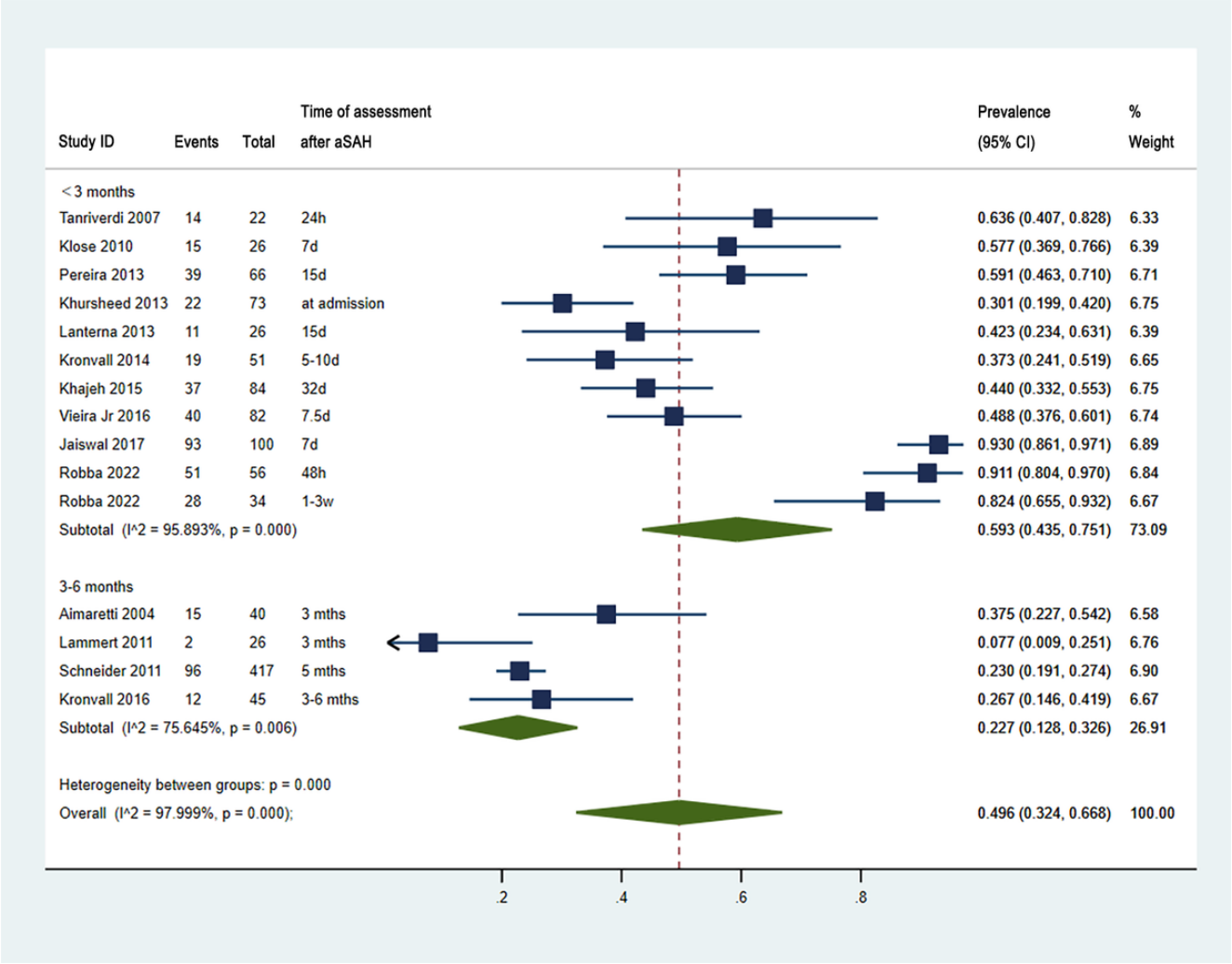

Figure 2

Pooled prevalence of PD in the acute phases after aSAH. CI, confidence interval.

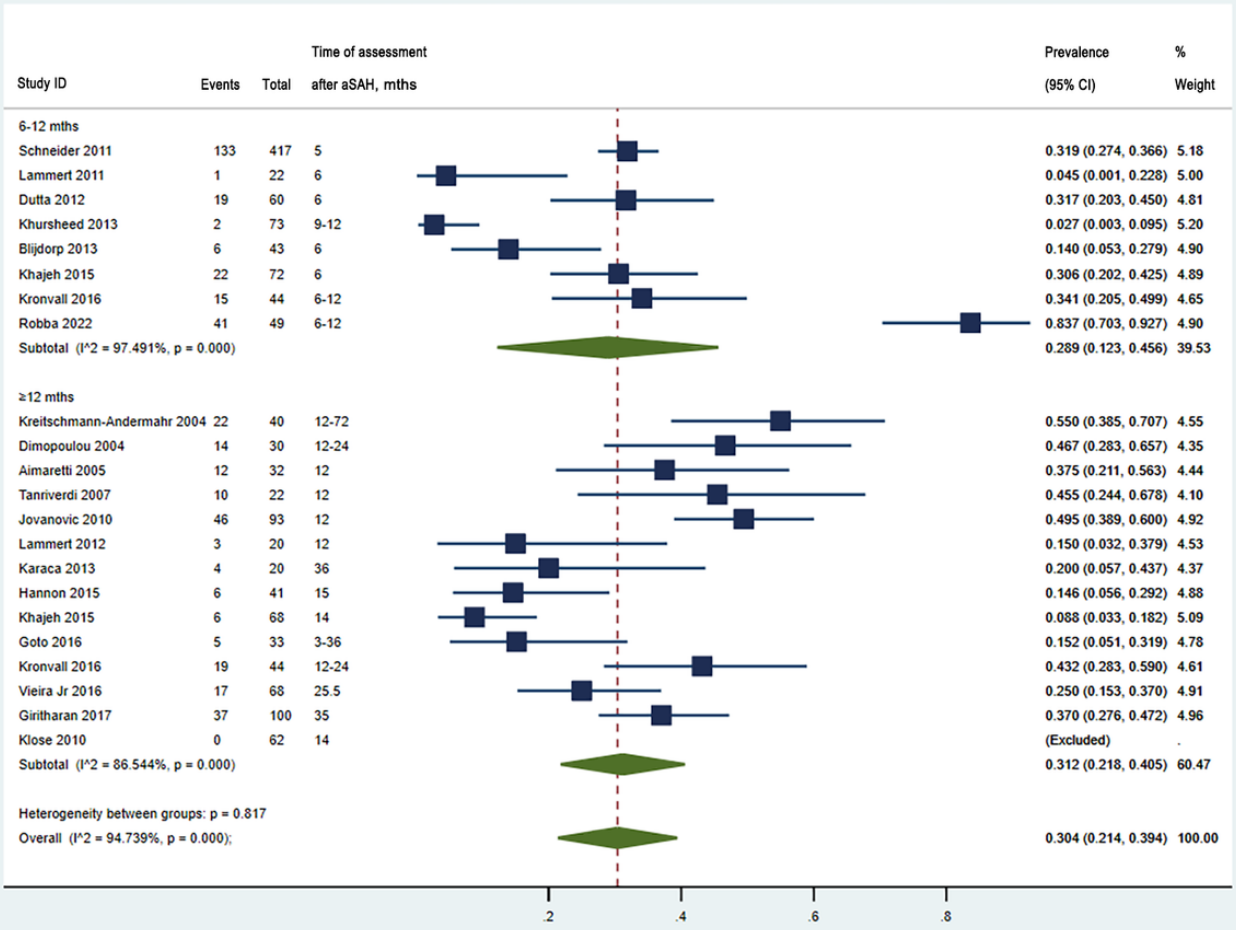

Figure 3

Pooled prevalence of PD in the chronic phases after aSAH. CI, confidence interval.

Supplementary Files

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- SupplementaryTable1.docx