HAPTOGLOBIN AFTER SUBARACHNOID HAEMORRHAGE: INDIVIDUAL PATIENT LEVEL DATA (IPLD) META-ANALYSIS

by

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ABSTRACT

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating subtype of stroke with high mortality and morbidity. aSAH has approximate incidence of 9 cases per 100,000 person-years, and approximately 1 in 6 patients die during the initial hemorrhage. Further, secondary injuries, including cerebral vasospasm and delayed cerebral infarct, are quite common after aSAH contributing to the overall mortality rate of nearly 50%. The goal of this study is to gain a better understanding of association between aSAH and Haptoglobin genotype (Hp) by conducting IPLD meta-analysis.

Data including 960 subjects from 11 studies were recruited from all published studies identified by Pubmed and Web of Science searches, including reference lists within publication, and unpublished studies identified via HATCH (Haemoglobin After in TraCranial Haemorrhage) consortium and the networks of individual consortium members by the 31st March 2016.

Given the individual patient level data available, both two-stage and one-stage meta-analysis were conducted. For two-stage meta-analysis, the primary outcomes were dichotomized as unfavorable and favorable outcome, and all secondary outcomes were binary outcomes. Logistic regression models were used in the first stage of two-stage meta-analysis to assess the association between Hp and aSAH recovery in each study. Generalized estimating equations (GEE) with exchangeable correlation were used to fit logistic regression model to estimate the

association between Hp and primary outcomes accounting for the correlations between repeated measurements over 1, 3, and 6 months for each study in the first stage. Logistic regression models were fit via maximum likelihood to assess the association in each study. In second stage, meta-analysis via random-effect models was conducted to obtain pooled odds ratio. Q tests and I^2 were used to test heterogeneity, and to measure possible inconsistency. Publication bias was assessed by funnel plots and using the Egger method. In one-stage analyses, mixed effects logistic regression was used to generate overall odds ratios using all individual level data from different studies simultaneously within one model.

Both two-stage and one-stage meta-analyses indicated there was no significant association between Hp and aSAH. Although Q tests showed there was no heterogeneity, I^2 in some studies were large, which indicated that the majority of the variability across studies were due to heterogeneity instead of chance. In the test of publication bias, both funnel plot and Egger test indicated there was no publication bias issue.

Public Health Significance: There were inconsistent findings from the literature regarding the association between Hp and outcome of aSAH. The work here investigates the relationship between haptoglobin genotype and outcomes after aSAH using meta-analysis based on current literature reports. While our findings were negative, there are a small number of studies with fairly small simple sizes, so results may still inform efforts at effective personalized preventive care and disease treatments with better specificity, targeted to the genetic makeup of each patient.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

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1.0 INTRODUCTION

1.1 ANEURYSMAL SUBARACHNOID HEMORRHAGE

In the United States, Subarachnoid hemorrhage (SAH) is responsible for 5% to 10% of all strokes and a greater loss of productive life. People of younger age are more likely to suffer SAH compared to other subtypes of stroke [1]. An intracranial aneurysm (also known as cerebral aneurysm) is a weakened, dilated area of a blood vessel in the brain that is prone to burst. The rupture of a cerebral aneurysm causes 85% spontaneous SAH. Although bleeding from small aneurysms causes most cases, larger aneurysms are more likely to rupture [2].

Aneurysmal subarachnoid hemorrhage (aSAH) is a subtype of devastating stroke that occurs at an early age. Because of initial bleeding and subsequent neurovascular events, aSAH has high mortality and morbidity [3, 4] with global health burden and permanent disability rates [5]. These events have a high mortality, with about 1/6 of aSAH patients dying during the initial bleed [6]. Severe headache of rapid onset, vomiting, decreased level of consciousness, fever, and seizures are all the common symptoms of aSAH [7]. Cerebral vasospasm (CV) and delayed cerebral ischaemia (DCI) are common and serious complications of aSAH, and together they contribute to the poor short-term (first month) outcomes profile after aSAH [8]. The long-term outcome and functional status after aSAH are poor with significant morbidity [8].

1.1.1 Epidemiology

The estimated overall incidence of aSAH is about 9 per 100,000 person-years. Japan (22.7 per 100,000 person-years), and Finland (19.7 per 100,000 person-year) have much higher rates than South and Central America (4.2 per 100,000 person-year), and other regions (9.1 per 100,000 person-year). Rates increase with increasing age, with age groups older than 85 years having the highest rate. Gender differences starts at age 55 years and increase thereafter. The overall incidence in women was 1.24 times higher than in men [9].

In the United States, the incidence of new cases of aSAH is about 30,000 per year [10]. From 1988 to 2010, the incidence of aSAH in the United States did not show a statistically significant increase ($p=0.22$), indicating stable incidence. However, 5-day, 30-day, and 90-day case-fatality rates have declined significantly over this time period. This reduction is likely due to advances in surgical and medical management, and systems-based changes including the emergence of neurocritical care units [3].

1.1.2 Assessment of Severity

Numerous tools, including the Hunt and Hess Scale, Fisher Scale, Glasgow Coma Score (GCS), and the World Federation of Neurological Surgeons Scale (WFNS) are used for assessment and prognostication of patients with aSAH. Most of these scales were derived retrospectively [11].

The GCS was originally designed to quantify responsiveness and clinical-exam after traumatic brain injury [12]. Since its initial development, it has been used as a standard tool to quantify neurologic status and changes in status in many populations.

WFNS is one of the most common scales. It quantifies burden based on focal neurological deficits and Glasgow Coma Scale (GCS), where higher grades are associate with worse outcomes. The GCS has less observer variability than WFNS, and is more commonly used in assessing the neurological status [11].

The Hunt and Hess scale grades subjects based on clinical examination upon admission and predicts outcome [13]. The Fisher scale assigns a grade based on the pattern of blood visualized on initial computed tomography (CT) scanning and predicts secondary injury (cerebral vasospasm) [11, 14].

1.2 HAPTOGLOBIN

As the most abundant protein in erythrocytes and blood, Haptoglobin (Hp) protein binds free hemoglobin and facilitates its removal from the bloodstream [15]. It is a unique acute phase protein that primarily scavenges haemoglobin (Hb) released into the circulation by haemolysis or normal red blood cell (RBC) turnover [16]. The Hp protein is encoded by two genes on chromosome 16; the Haptoglobin α and β gene. The gene for the β-chain has no known genetic variability. However, the gene for the α-chain has two common alleles, α-1 and α-2 [17]. A common 1.7kb copy number variant (CNV) inside the HP gene determines the copy number of a tandem two-exon segment including sequence that encodes a multimerization domain [18].

In human populations, the α-chain alleles 1 and 2 of haptoglobin (Hp) molecule account for three common genotypes and phenotypes: the homozygous Hp1-1 (dominant), Hp2-2 (recessive) and the heterozygous Hp2-1. These three phenotypes, which determined by two alleles Hp1 and Hp2, have biologically significant difference in their antioxidant, scavenging,

and immunomodulatory properties and may therefore influence the course of inflammatory disease [16, 19]. In most cases, the Hp2 is a less efficient antioxidant than Hp1, and is required to make the tight-junction modulator protein zonulin, which is the preprocessed product of Hp2 [18]. As aSAH is a condition where there is significant blood outside the vasculature and initiates a strong inflammatory response, many groups have set out to determine the role genetic variability in the Hp gene has on short and long term recovery after aSAH.

1.3 GOAL

Hp gene polymorphism effects have been reported prominently in the literature exploring outcomes after aSAH. While some studies have found the Hp-2 allele associates with worse recovery [20-23] there are inconsistent findings from the literatures [24]. The goal of this study is to investigate the relationship between haptoglobin genotype and outcomes after aneurysmal subarachnoid hemorrhage. Meta-analysis will be used in examining associations from the current literatures. Both two-stage and one-stage meta-analysis will be used. In two-stage analysis, Generalized Estimating Equation (GEE) will be used to fit logistic regression models to assess the odds ratio in each study controlling for important demographics and clinical variables in primary outcomes, which are observed at multiple time points, and maximum likelihood will be used to fit logistic regression models to assess the secondary outcomes, which are assessed at one time per-subject. The results from each individual study will be pooled together in the second stage analysis. One-stage meta-analysis will be also conducted to examine the association between Hp and outcome after aSAH given the availability of individual patient level data.

2.0 METHODS

2.1 STUDY DESIGN AND SUBJECTS

This study is a retrospective study and includes data collected from 11 studies who satisfied criteria including: (1) subjects with diagnosis of aSAH; (2) subject who are at least 18 years old; (3) haptoglobin genotype or phenotype available; (4) outcomes were measured within 1 month (+/- 2 weeks), 3 months (+/- 1.5 months) and 6 months (4.5 months to 12 months) of the aSAH (if more than one outcome is available within each of these time frames, the one closest to 1, 3 or 6 months will be utilized). Data was extracted from all published studies identified by Pubmed and Web of Science searches, including reference lists within publication, and unpublished studies identified via the HATCH (Haemoglobin After in TraCranial Haemorrhage) consortium and the networks of individual consortium members by the 31st March 2016.

Initial study data included information from available electronic medical records. These data included demographic information such as age, gender and race. Subjects outcomes, including Glasgow Outcome Score (GOS) and Modified Rankin Score (mRS) were measured 1 month, 3 months and 6 months. Data for analysis consisted of 960 subjects from 11 studies. Only 21 subjects had conservative aneurysmal treatment and were excluded from our analysis.

Analysis with different comparisons of Hp genotype were conducted (Hp-22 vs Hp-11 & Hp-21, Hp-11 vs Hp-21 & Hp-22; Hp-11 vs Hp-22; Hp-22 vs Hp-21; Hp-21 vs Hp-11). For

primary outcomes, both longitudinal analysis and cross-sectional analysis at each time points were conducted. This paper will focus on the effect of Hp-22 versus Hp-11 and Hp-21 on aSAH with longitudinal analysis on primary outcomes and cross-sectional analysis on secondary outcomes.

2.2 INDEPENDENT VARIABLES

2.2.1 Demographic variables

- **Age, gender and race**

All subjects were at least 18 years old with average age of 54.33 and there were slight difference across studies. The average age of the subjects in study B was greatest (62.14) and study E was youngest group (50.76). There were slightly more females than males in this whole study: 31.16% male and 68.85% female, as is common in aSAH. Most subjects were white/caucasian (70.56%). However, there were some minorities: black (15.28%), Asian (11.46%), and 2.7% subjects reported of ‘other’ race.

- **Aneurysmal Treatment**

The most common treatments of cerebral aneurysms are neurosurgical clipping and endovascular coiling. These treatments have similar outcomes, but the influence of these treatment modalities is still judged controversially [25]. Historically, early surgical treatment was thought to decrease angiographic vasospasm and delayed ischemic neurological deficit (DIND) by removing subarachnoid blood [26]. However, some studies showed no significant difference in the degree of angiographic vasospasm between the surgical and other treatments. It has been suggested that

the effect of clot removal may be offset by the negative aspect of early surgery, like brain retraction [26, 27].

Aneurysmal treatment is a main covariate in this study. Most subjects received neurosurgical clipping or endovascular coiling, and only 21 subjects received conservative treatment. In this study, subjects with conservative treatment, who have worse outcomes, were removed and the analysis only focused on subjects with endovascular or surgical treatment.

- **Aneurysmal Sites**

Among patients with aSAH, the location of aneurysm was classified in 5 categories: (1) the anterior communicating artery (AcoA); (2) the distal anterior cerebral artery (ACA); (3) the internal carotid artery (ICA); (4) the middle cerebral artery (MCA); (5) the vertebrobasilar artery (VBA). Without considering age, ACoA aneurysms are more common in men, whereas ICA aneurysms are more likely to happen among women [28, 29].

In this study, we had aneurysm site data from 882 subjects. Among these subjects, the majority were ICA (26.98%) and ACA (40.14%) aneurysms, and 32.88% of aneurysms were from MCA (16.44%) and VBA (16.44%).

- **Diabetes**

Diabetes mellitus (DM) is a group of metabolic disorders in which there are high blood glucose levels over a prolonged period [30]. It is reported that the diabetic patients have 1.7 times higher probability to have cerebrovascular disease than nondiabetic persons. However, some studies reported a decreased association between diabetes mellitus and aSAH risk [31]. The healthier lifestyle DM patients have may be the reason for the lower risk [32]. Only 9.26% subjects in this study with DM, which is much lower than subjects without.

- **Hypertension**

Hypertension (HTN) is defined by the presence of persistently elevated blood pressure, which usually leads to morphological and functional changes in the heart and systemic arterioles [33]. From the numerous studies of aSAH, HTN is one of the most controvertible factor to cause aSAH. However, according to multivariate analysis, HTN is not an independent risk factor for aSAH [34]. In this study, about half subjects had HTN (46.24%). Study E had the least HTN patients with only 26.63% of the total.

2.2.2 Clinical variables

- **Glasgow Coma Score (GCS)**

The GCS is a common tool to quantify neurologic function in acutely ill or injured patients. It was originally designed to assess level of consciousness after traumatic brain injury [12], but it is now used in many other populations with potential brain injury. The GCS assigns numeric scores to a patient best eye opening, verbal and motor response in response to stimuli. GCS ranges 3 (deep coma) to 15 (awake and alert).

- **Fisher Grade**

The Fisher Grade is widely accepted in assessment of the extensiveness of aSAH and the presence of other intracranial hemorrhage on the CT scan [14]. The Fisher Grade assigns individuals to one of four broad outcome categories: Grade 1- no SAH visualized; Grade 2 – thin layer of SAH, less than 1 mm thick; Grade 3 – focal or diffuse layer of SAH, greater than 3 mm in thickness; Grade 4 – intracerebral or intraventricular clots with or without SAH [35]. In this study, we adjusted Fisher Grade by combing grade 1 and 2 as one group, and grade 3 and 4 as a second group. There are only 20.2% subjects without or with thin layer of SAH in our analysis.

- **World Federation of Neurosurgical Societies (WFNS)**

WFNS grading system is a five-step grading scale based on a preoperative clinical condition for predicting further outcomes. In 1988, the grading scale was established by the Executive Committee of WFNS. There are 5 grades in WFNS, and the increasing grade is associated with worse outcome. For example, grade V denotes strongly predictive for extremely poor outcome [36].

In this study, WFNS was dichotomized into good grade (WFNS 1 - 3) which indicates a favorable outcome or poor grade (WFNS 4 - 5) which indicates a poor outcome. There were 837 subjects in this study with WFNS, and 71.68% of them had a good grade.

- **Hunt and Hess (H&H)**

Hunt and Hess is a commonly used way to assess the clinical severity of SAH [37]. The H&H quantifies disability using an ordinal hierarchical grading from zero to 5, and the increasing grade is associated with worse outcome. Patients with severe H&H (4 and 5) have fared poorly and generally consist of approximately 20% - 30% of those admitted to the hospital with aSAH [38].

In this study, H&H was dichotomized into good grade (H&H 0-3) and poor grade (H&H 4-5). There were 140 (27.66%) patients in the study with H&H and 366 (72.34%) with good outcome.

2.3 OUTCOME VARIABLES

2.3.1 Primary Outcome

- **Modified Rankin Scale (mRS)**

The mRS is one of the most prevalent functional outcome measure in contemporary stroke trials and the most common measure in landmark studies. The mRS quantifies disability using an ordinal hierarchical grading from zero to six, and the increasing grade indicates poorer outcome. Zero indicates no symptoms and 6 indicates death [39].

In this study, the outcome variable of interest was 1, 3, and 6-month mRS. The mRS was dichotomized into favorable (mRS 0-2 [good recovery, no significant disability, slight disability]) or unfavorable (mRS 3-6 [moderate disability, moderately severe disability, severe disability, or death]) as is often done in the aSAH literature to maximize power. In studies A, B, C, D, F, G, and I there was information on mRS, and we used it as the primary outcome in our analysis.

- **Glasgow Outcome Scale (GOS)**

The GOS is one of the most widely used outcome measure after traumatic brain injury in clinical settings because it is easy to administer. GOS uses an ordinal hierarchical grading and is divided into five categories: dead, vegetative state, severe disability, moderate disability, and good recovery. The increasing grade indicates better outcome [40].

In this study, the outcome variable of interest was 1, 3, and 6-month GOS. The GOS was dichotomized into favorable (GOS 4-5 [moderate disability or good recovery]) or unfavorable (GOS 1-3 [death, vegetative state, or severe disability]) as is often done in the literature to

maximize power. Study A, C, D, E, F, G, and I had information of GOS, and we used them in further analysis.

The primary outcome was defined mainly as mRS, which was used in most analysis. However, Study E used GOS as primary outcome because it didn't have mRS information. In this study, mRS in Study A, B, C, D, F, G, I and GOS in Study E were combined in the analysis of the primary outcome.

2.3.2 Secondary Outcomes

aSAH may induced cerebral vasospasm, a decrease in the internal lumen of the cerebral blood vessels that is commonly diagnosed with angiography. About 30% - 70% aSAH patients have angiographic cerebral vasospasm, and about 50% of them have delayed neurologic ischemia resulting in permanent deficits from ischemic stroke or death [41].

- **The presence of Delayed Ischemic Neurological Deficit (DIND)**

DIND, resulting from cerebral vasospasm, is common after aSAH and contributes to the high morbidity and mortality [42, 43]. DIND is defined as a new focal neurologic deficit or a drop in GCS of greater than 2 not temporally related to the treatment of the aneurysm and not due to other cases, such as hyponatremia, infection and others. The biological process underlying DIND remains unclear, but some studies suggest that DIND is induced by cerebral vasospasm and additional factors after SAH. Patients that develop DIND always have higher Hunt and Hess grade and more often are classified as Fisher Grade 3 [43].

In our study, less than half (35.87%) of the subjects had DIND. Study A, B, C, D, G, and I had DIND information, and we did analysis in these studies.

- **The presence of Radiological Infarct after aSAH**

Silent infarction is common in aSAH patients, and always associated with poor outcome. It can be detected by invasive neuromonitoring devices because of the changes in cerebral metabolism and oxygenation. Compared those with distant or no ischemia, patients with infarction have lower lactate-pyruvate-ration elevation and brain glucose. These concepts are used as evidence in clinical research [44] but radiographic evidence (CT or magnetic resonance imaging) of infarction is used for clinical care. For this analysis, Radiographic Infarction was verified based on CT or MR evidence of ischemia

In this study, about 30% subjects had the presence of radiological infarct, and Study A, B, C, D, and G had this data.

- **The presence of angiographic evidence of vasospasm**

Vasospasm, a reduction of the internal lumen of the cerebral blood vessels, results in reduced blood flow and an increase in blood flow velocity after aSAH. The clinical vasospasm includes vasospasm identified by angiography or transcranial doppler ultrasonography and new onset of neurologic deficit and contributes to delayed ischemic neurologic deficit; and delayed cerebral ischemia [45].

Delayed cerebral ischemia (DCI) is a specific subtype of ischemic stroke among patients who survive from aneurysmal subarachnoid hemorrhage. This stroke usually develops about one week after aneurysm rupture. Studies confirmed an association between DCI and angiographic vasospasm [46], and prevention or treatment of angiographic vasospasm after aSAH may mitigate its sequelae [47].

In this study, about 40% subjects had the presence of angiographic evidence of vasospasm, which is a little bit higher than the presence of DIND and radiological infarct. Study A, D, E, F, G, and I had this data.

- **The presence of Transcranial Doppler Sonography (TCD) evidence of vasospasm**

TCD is a noninvasive ultrasound diagnostic method to monitor the state of intracerebral hemodynamics [45]. It is used to quantify cerebral blood flow velocity in the large cerebral blood vessels and may infer cerebral vasospasm. However, because of high rate of false negative results likely due to micro vessel vasospasm and not detected with TCD, there are many criticisms about TCD's detecting ability.

In this study, we defined subjects with "definite vasospasm" as TCD higher than 200cm/s as vasospasm. Around 40% patients had the presence of TCD evidence of vasospasm based on our criteria, which is almost same as the percentage of presence of angiographic evidence of vasospasm. Study B, C, D, F, I, J, and K had data of this information,

2.4 DATA ANALYSIS

Data were from 11 different studies and were merged into a single file with variable coding standardized (e.g. female sex=1) for each individual. Upon receiving the Excel file containing the raw data, data management and analysis were done, including a comprehensive review of all raw data, cleaning of the dataset and performing all statistical analysis including modelling and graphical analysis.

Statistical analyses were performed in STATA software (version 14.0 SE StataCorp, College Station, TX). Descriptive analysis included computing means and standard deviation for

all continuous variables, and frequencies and percentages for all categorical variables in each study.

Two-stage and one-stage meta-analysis were conducted. In the first step of two-stage analyses, the primary outcome mostly uses mRS except Study E which uses GOS. GEE was used to fit logistic regression models in analysis of the primary outcome because of repeated measurements. Secondary outcomes were only measured once so logistic regression models were fit via maximum likelihood. Instead of simply dichotomizing primary outcomes at one fixed point, sensitivity analysis including a sliding dichotomy and proportional odds logistic regression model were also conducted for the primary outcome, with the aim of avoiding information loss about the outcome and reducing statistical power. Meta-analysis with random-effects was used in the secondary step. In the diagnosis of meta-analysis, the heterogeneity was tested by Q tests and I2, and publication bias was measured by funnel plot and Egger's test.

In the one-stage analyses, mixed effect logistic regression models were used to generate overall odds ratios by utilizing all the data from all studies in one step adjusting for the covariates. In both primary and secondary outcomes, each study was considered as a cluster. In the primary outcomes, each subject was also considered as a cluster because of repeated measurements.

In the adjusted analysis after controlling other covariates, the following minimal core covariates were used: 1. Age; 2. Fisher, dichotomized into 1+2 and 3+4. 3. WFNS dichotomized into good and poor grade; 4. Treatment, categorized into clipping and coiling; and 5. Time (used in longitudinal modelling). Where possible, allowing for sample size and data availability, additional covariates will be used, prioritized in the following order: 1. Diabetes; 2. Hypertension; 3. Race; and 4. Aneurysm site.

2.4.1 Hardy-Weinberg equilibrium

Hardy-Weinberg equilibrium is used to describe the relationship between allele frequency and genotype frequency in a population. OEGE (Online Encyclopedia for Genetic Epidemiology studies) was used to test if Hp in all studies follow the Hardy-Weinberg equilibrium. Chi-square Hardy-Weinberg equilibrium test calculator for biallelic markers (SNPs, indel etc), including analysis for ascertainment bias for ascertainment bias for dominant/recessive models (due to biological or technical causes) was used. P-values were calculated with 1 degree of freedom.

2.4.2 Longitudinal Modelling

The longitudinal study is a research design that involves repeated observations of the same variables over a periods of time [48]. In a longitudinal study, the outcome has been measured several times, and the result of each in one subject is correlated.

GOS and mRS were measured three times (1 month, 3 months, and 6 months) in this study, so longitudinal analysis was needed. For each subject, the result of mRS or GOS in different time point were correlated. If both mRS and GOS were available for the same dataset, mRS will be used.

2.4.3 Generalized Estimating Equation (GEE)

The GEE, which was introduced by Liang and Zeger (1986), is a method that can be used to estimate marginal or population-averaged effects taking into account the dependence among observations within a subject. It is usually done by specifying working correlations R_i for the

observed outcomes (conditional on covariates). In this study, with many clusters (960 subjects) and relatively few observations per cluster (1, 3, and 6 months per subject), the GEE method was used to adjust replicated primary outcomes within subjects at three time points in the first stage of the two-stage meta-analysis. However, the GEE method is limited to a single level of clustering, so it cannot be used in one-stage meta-analysis in this study.

The formulation of a model of mean μ_{ij}, which indicate the subject i at time j, depends upon regression parameters β_k, and variance structure V_i is as following [49]:

$$U(\beta) = \sum_{i=1}^{N} \frac{\partial \mu_{ij}}{\partial \beta_k} V_i^{-1} \{Y_i - \mu_i(\beta)\}$$

The GEE is based on the concept of estimating equations and provides a general approach to analyze correlated responses, and this idea is to generalize the cross-sectional likelihood estimating equations of a Generalized Linear Model (GLM) by incorporating the covariance matrix of the responses. Using the GEE approach, we do not need to specify a model for the whole multivariate distribution of the data. Instead, it models the mean response $E(Y_i)$ and the covariance matrix V_i as in the normal case.

A feature of GEE is that marginal effects can be consistently estimated, even if the dependence among observations within subjects working correlations R_i is not properly specified. However, GEE does assume that the model for the mean is correct. Misspecification of the mean model could lead to biased results.

In the analysis of the relationship between Hp and mRS or GOS, GEE was used to estimate odds ratio between different Hp genotypes and primary outcome. The family was

binomial because the outcome was binary (1-unfavorable; 0-favorable), and the logit link was used.

2.4.4 Mixed Model

A mixed model is a statistical model containing both fixed effects and random effects. The process for fitting the mixed model involves estimating the fixed effects, estimating the random effects and estimating the variance parameters.

In this study, mixed effect logistic regression models were used in one-stage analysis. Each study was considered as a cluster in analysis. The primary outcomes were in a longitudinal dataset with three time points, and each subject was also considered as a cluster.

2.4.5 Logistic regression

Logistic regression was used to model the dichotomous/binary outcomes. Given a probability p, the logit is defined as

$$\text{logit(p)} = \log\left(\frac{p}{1-p}\right) = \log(p) - \log(1-p) = -\log(\frac{1}{p} - 1)$$

Since $\frac{p}{1-p}$ is what defined as the odds, the logit is also known as the log-odds. There is a one-to-one correspondence between p and logit(p).

Given a value of a logit(p) = θ, the probability can be computed. The inverse of the logit is known as the expit:

$$\text{expit}(\theta) = \frac{e^{\theta}}{1 + e^{\theta}}$$

In cross sectional analysis of secondary outcomes and some primary outcomes with one time point, the time effect was not considered. The logistic regression model is used in this analysis to find the odds ratio between different Hp.

2.4.6 Sliding Dichotomy

In the previous analysis, the mRS and GOS were divided into two groups: mRS 0-2 to 3-6 and GOS 1-3 to 4-5, and all subjects dichotomized at the fixed point. The statistical analysis and interpretation of the results are simple, but with issue of loss of information about outcome and reduced statistical power [50].

One method has been proposed to avoid these problem is the sliding dichotomy. A single binary outcome, as assessed by the GOS or mRS, dichotomized into favorable and unfavorable using a cut point depending on the predicted prognosis for an individual patient on entry into the study. For example, only a good recovery might be considered as favorable outcome for a patient predicted to have a good recovery; similarity, severe disability might be regarded as a favorable outcome for a patient predicted to die or be in a vegetative state [50]. If both mRS and GOS are available for the same dataset, mRS will be used. Regarding analysis, we first estimated the baseline prognostic risk in each patient by calculating the probability of a favorable outcome using a predictive model with the covariates (listed above) adjusted for in each data set in a logistic regression model. Then, patients were grouped into three prognostic cluster of approximately equal sample size based on the tertiles of prognostic scores: best, intermediate, and worst prognosis.

For each band, a separate cut point on either the GOS or the mRS was defined and a new outcome variable was created. For a sliding or logical cut point, favorable outcome was defined in the worst tier as score 3-5 in GOS; 4-5 in the intermediate tier, and only 5 in best tier. For the mRS, favorable outcome in the worst tier included good recovery, no significant disability, slight disability, moderate disability, and moderately severe disability; good recovery, no significant disability, slight disability, and moderate disability in intermediate tier; and good recovery, no significant disability, and slight disability in the best tier [50]. Binary logistic regression was used, with stratification by prognostic bands. The pooled sliding dichotomy odds ratio was calculated as the summary effect of Hp on outcomes.

2.4.7 Proportional odds logistic regression model

Proportional odds logistic regression is another way to avoid theoretical issues. It can be used to estimate the covariate effects and the relative probabilities of outcomes in ordinal categories variable.

The ordinal mRS and ordinal GOS were analyzed separately: For patients with mRS outcome, the ordinal mRS was considered in a 5 point ordinal scale (mRS larger or equal to 4 were combined into one level); For patients with GOS outcome, the ordinal GOS was considered in a 3 point ordinal scale (GOS less or equal to 3 were combined into one level). The proportional odds logistic regression model was used in this analysis. The proportional odds logistic regression estimates a common odds ratio for each of the possible cut points of the outcome scale [50]. The common odds ratio is formally valid if the odds ratios for each cut point are the same. The common odds ratio can be interpreted as a summary measure of Hp effect on outcomes.

2.4.8 Meta-Analysis

The meta-analysis is a statistical analysis that combines the results of several independent studies and derive a pooled estimate to get an common result [51]. With the odds ratio of Hp effect on outcomes in each study, Meta-Analysis was used to get the common odds ratio among all studies centers.

There are fixed (common) effect meta-analysis and random effect meta-analysis. In fixed effect analysis, it is assumed that the effect of Hp is the same across different studies. But in random effect analysis, it is assumed that the true effect of Hp in each study is randomly, normally distributed between studies. To estimate the between-study variance τ^2 and modify the weights in each study, the DerSimonian and Laird estimate is mostly used. The equation of random effect estimate is as following.

$$log\ OR_R = \frac{\sum_{i=1}^{k} w_i^* log\ OR_i}{\sum_{i=1}^{k} w_i^*}$$

Where,

$$w_i^* = \frac{1}{v_i + \hat{\tau}^2}$$

And the variance of random-effects summary OR is.

$$\frac{1}{\sum_{i=1}^{k} w_i^*}$$

This study used Meta-analysis of individual participant data (IPD), which obtained and synthesized the raw individual level data from multiple related studies. This approach is becoming an increasingly popular tool as an alternative to traditional aggregate data Meta-

analysis [52]. There are both statistical and clinical advantages of this approach, including increasing the power to detect differential treatment effects across individuals in randomized trials, and allowing adjustment for confounding factors in observational studies [53]. Also, the subgroup effects at an individual level can be examined [54]. It is most used when a Meta-analysis of aggregate data cannot reliably answer the clinical questions, with aim to summarize the evidence on a particular clinical question from multiple related studies [53]. For example, this study was focused on whether Hp genotype effects the outcome after aSAH.

There are some requirements of individual participant data for Meta-analysis. Firstly, it should be protocol based, clearly reported, driven by clinical questions. Secondly, this statistical implementation must preserve the clustering of patients within studies. Analyzing IPD as if they all came from a single study is inappropriate and will cause some problems.

Two statistical approaches including one-stage and two-stage are commonly used in IPD Meta-analysis. Two-stage analysis considers each study independently by appropriate model and combines these in a traditional Meta-analysis model. Two-stage approach is more laborious, but easier to be understand because it uses standard Meta-analysis methods in the second step [52, 53].

One-stage approach conveniently requires only a single model and analyzes all studies simultaneously, which may increase complexity for non-statisticians and requires careful separation of within study and between study variability. However, this approach uses a more exact likelihood specification, which avoids the assumption of within-study normality and known within-study variance. It is commonly used in small studies and/or rare events [52, 53].

The result of one-stage and two-stage approach may different and most of difference are result of different modelling assumptions, which including the specification of the likelihood and

included parameters, the choice of random or fixed effects. Meanwhile, choosing a different estimation procedure is another reason for this difference. However, these two approaches will result very similar conclusions when the same assumptions are made and the same estimation procedures are used [52].

The usual test (Q test) and I^2 are two common ways to test the heterogeneity and conclude consistency of meta-analysis. The statistic of Q test follows χ^2 distribution with k-1 degree of freedom where k is the number of studies. The I^2 is the degree of inconsistency in the study's results which is an alternative approach to quantify the effect of heterogeneity. I^2 describes the percentage of total variation across studies that is due to heterogeneity rather than chance, and it is obtained as I^2=100%*(Q-df)/Q, where Q is Cochran's heterogeneity statistics. I^2 always between 0% and 100%, and the heterogeneity increases with larger values. When I^2 is 0% means no heterogeneity is observed [55]. There are widely used benchmarks for I^2. For example, I^2 values of 25%, 50%, and 75% are always interpreted as representing small, moderate and high level of heterogeneity.

In STATA, heterogeneity is calculated by following formula.

$$Q = \sum_i \frac{1}{\sigma_i} * (effect(i) - effect\_pooled)^2$$

Where,

$$\sigma_i = ((upper\ limit - lower\ limit)/(2 * z))^2$$

Publication bias occurs when considering the representativeness of any given study or set of studies that have significant outcome as these are more likely to be published. Tests for the asymmetry of funnel plots and methods based on selection models are the most common types of

the statistical methods that assess the publication bias. In this study, both funnel plot and Egger's regression method were used [56].

A Funnel plot is a graph designed to check for the existence of publication bias and is commonly used in systematic review and meta-analysis. In the absence of publication bias, it assumes that the largest studies will be plotted near the average, and smaller studies will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias. A funnel plot is a scatterplot of treatment effect against a measure of study size. It is used primarily as a visual aid for detecting bias for systematic heterogeneity. A symmetric inverted funnel shape arises from a "well-behaved" data set, which is not likely to have publication bias. On the contrary, an asymmetric funnel indicates a relationship between treatment effect estimate and study size. This suggests the possibility of either publication bias or a systematic difference between smaller and larger studies.

Asymmetry can also arise from use of an inappropriate effect measure. Whatever the cause, an asymmetric funnel plot leads to doubts over the appropriateness of a simple meta-analysis and suggests that there needs to be investigation of potential causes. The asymmetry of funnel plot can be tested by Egger's regression method, which is algebraically identical to a test that there is no linear association between the treatment effect and its standard error and indicate that there is no straight-line association in the funnel plot of treatment effect against its standard error.

3.0 RESULT

3.1 DESCRIPTIVE CHARACTERISITICS

3.1.1 Demographics

A detailed description of the demographics variables by study group assignment is presented in Table 1, which including: age, gender, admission WFNS, fisher grade on initial CT, aneurysmal treatment. The age of subjects was 54.34 with standard deviation 13.09. Other descriptive characteristics of demographics variables were shown in Table 1. Table 1 also indicated that there was missing data for several variables.

Table 1. Descriptive statistics for demographics variables

	A (n=37)	B (n=95)	C (n=86)	D (n=55)	E (n=169)	F (n=143)	G (n=46)	H (n=37)	I (n=192)	J (n=30)	K (n=49)	All (n=939)
age												934 (99.47%)
Mean (SD)	59.49 (13.0)	62.14 (13.74)	54.36 (14.34)	54.14 (12.93)	50.76 (11.61)	53.70 (13.91)	53.49 (12.92)	52.49 (15.66)	54.42 (11.16)	51.53 (12.80)	53.20 (11.23)	54.34 (13.09)
Sex												934 (99.47%)
Male	13 (35.14%)	42 (44.21%)	26 (30.23%)	13 (23.64%)	57 (33.73%)	36 (26.09%)	14 (30.43%)	14 (37.84%)	55 (28.65%)	10 (33.33%)	11 (22.45%)	291 (31.16%)
Female	24 (64.86%)	53 (55.79%)	60 (69.77%)	42 (76.36%)	112 (66.27%)	102 (73.91%)	32 (69.57%)	23 (62.16%)	137 (71.35%)	20 (66.67%)	38 (77.55%)	643 (68.84%)
WFNS												837 (89.14%)
0	12 (32.43%)	57 (60.00%)	55 (63.95%)	34 (61.82%)	155 (91.72%)	87 (62.59%)	31 (70.45%)	17 (85.00%)	152 (79.17%)	0 (0.00%)	0 (0.00%)	600 (71.68%)
1	25 (67.57%)	38 (40.00%)	31 (36.05%)	21 (38.18%)	14 (8.28%)	52 (37.41%)	13 (29.55%)	3 (15.00%)	40 (20.83%)	0 (0.00%)	0 (0.00%)	237 (28.32%)
Fisher												901 (95.95%)
0	0 (0.00%)	9 (9.57%)	7 (8.14%)	12 (21.82%)	45 (26.63%)	50 (36.50%)	3 (5.82%)	2 (25.00%)	54 (28.13%)	0 (0.00%)	0 (0.00%)	182 (20.20%)
1	37 (100%)	85 (90.43%)	79 (91.86%)	43 (78.18%)	124 (73.37%)	87 (63.50%)	41 (93.18%)	6 (75.00%)	138 (71.88%)	30 (10.00%)	49 (100.00%)	719 (79.80%)

Table 1 Continued

	A (n=37)	B (n=95)	C (n=86)	D (n=55)	E (n=169)	F (n=143)	G (n=46)	H (n=37)	I (n=192)	J (n=30)	K (n=49)	All (n=939)
Treatment												889 (94.68%)
endovascular	32 (86.49%)	22 (23.16%)	41 (47.67%)	35 (63.64%)	143 (85.12%)	25 (20.00%)	31 (67.39%)	3 (50.00%)	115 (59.90%)	13 (43.33%)	17 (34.69%)	477 (53.66%)
surgical	5 (13.51%)	73 (76.84%)	45 (52.33%)	20 (36.36%)	25 (14.88%)	100 (80.00%)	15 (32.61%)	3 (50.00%)	77 (40.10%)	17 (56.67%)	32 (65.31%)	412 (46.34%)
Aneurysm												882 (93.93%)
ICA	3 (8.11%)	30 (31.58%)	24 (27.91%)	9 (16.36%)	44 (26.04%)	45 (34.62%)	18 (40.91%)	5 (19.23%)	55 (28.65%)	0 (0.00%)	5 (10.42%)	238 (26.98%)
ACA	15 (40.54%)	34 (35.79%)	30 (34.88%)	28 (50.91%)	77 (45.56%)	47 (36.15%)	13 (29.55%)	11 (42.31%)	78 (40.63%)	0 (0.00%)	21 (43.75%)	354 (40.14%)
MCA	13 (35.14%)	18 (18.95%)	8 (9.30%)	9 (16.36&)	32 (18.93%)	18 (13.85%)	3 (6.82%)	4 (15.38%)	25 (13.02%)	0 (0.00%)	15 (31.25%)	145 (16.44%)
vertebral-basilar	6 (16.22%)	13 (13.68%)	24 (27.91%)	9 (16.36&)	16 (9.47%)	20 (15.38%)	10 (22.73%)	6 (23.08%)	34 (17.71%)	0 (0.00%)	7 (14.58%)	145 (16.44%)
HTN												865 (92.12%)
No	18 (48.65%)	43 (45.26%)	37 (43.53%)	27 (49.09%)	124 (73.37%)	52 (39.10%)	19 (42.22%)	2 (25.00%)	114 (62.30%)	18 (60.00%)	11 (44.00%)	465 (53.76%)
Yes	19 (51.35%)	52 (54.74%)	48 (56.47%)	28 (50.91%)	45 (26.63%)	81 (60.90%)	26 (57.78%)	6 (75.00%)	69 (37.70%)	12 (40.00%)	14 (56.00%)	400 (46.24%)

3.1.2 Clinical Outcome

All primary and secondary outcome data were categorical data, and Table 2 showed the frequency and percentage of each category for each study and the table across all studies.

Table 2. Descriptive statistics for clinical outcome

	A (n=37)	B (n=95)	C (n=86)	D (n=55)	E (n=169)	F (n=143)	G (n=46)	H (n=37)	I (n=192)	J (n=30)	K (n=49)	All (n=939)
mRS30d												372 (44.20%)
0	0 (0.00%)	22 (23.16%)	0 (0.00%)	9 (21.43%)	0 (0.00%)	7 (6.31%)	7 (18.42%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	45 (12.10%)
1	0 (0.00%)	23 (24.21%)	8 (9.30%)	16 (38.10%)	0 (0.00%)	22 (19.82%)	11 (28.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	80 (21.51%)
2	0 (0.00%)	15 (15.79%)	5 (5.81%)	3 (7.14%)	0 (0.00%)	25 (22.52%)	5 (13.16%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	53 (14.25%)
3	0 (0.00%)	7 (7.37%)	33 (38.37%)	6 (14.29%)	0 (0.00%)	21 (18.92%)	3 (7.89%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	70 (18.82%)
4	0 (0.00%)	16 (16.84%)	16 (18.60%)	5 (11.90%)	0 (0.00%)	18 (16.22%)	8 (21.05%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	63 (16.94%)
5	0 (0.00%)	11 (11.58%)	14 (16.28 %)	3 (7.14%)	0 (0.00%)	5 (4.50%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	35 (9.41%)
6	0 (0.00%)	1 (1.05%)	10 (11.63%)	0 (0.00%)	0 (0.00%)	13 (11.71%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	26 (6.99%)
mRS3m												531 (56.55%)
0	0 (0.00%)	32 (33.68%)	2 (2.38%)	9 (21.43%)	0 (0.00%)	9 (15.52%)	4 (16.00%)	0 (0.00%)	34 (17.71%)	0 (0.00%)	0 (0.00%)	90 (16.95%)
1	7 (20.00%)	12 (12.63%)	24 (28.57%)	16 (38.10%)	0 (0.00%)	23 (39.66%)	6 (24.00%)	0 (0.00%)	57 (29.69%)	0 (0.00%)	0 (0.00%)	145 (27.31%)

Table 2 Continued

2	13 (37.14%)	13 (13.68%)	13 (15.48%)	3 (7.14%)	0 (0.00%)	10 (17.24%)	3 (12.00%)	0 (0.00%)	45 (23.44%)	0 (0.00%)	0 (0.00%)	100 (18.83%)
3	8 (22.86%)	13 (13.68%)	18 (21.43%)	6 (14.29%)	0 (0.00%)	6 (10.34%)	6 (24.00%)	0 (0.00%)	16 (8.33%)	0 (0.00%)	0 (0.00%)	73 (13.75%)
4	4 (10.81%)	11 (11.58%)	11 (13.10%)	5 (11.90%)	0 (0.00%)	4 (6.90%)	3 (12.00%)	0 (0.00%)	6 (3.13%)	0 (0.00%)	0 (0.00%)	44 (8.29%)
5	2 (5.71%)	12 (12.63%)	6 (7.14%)	3 (7.14%)	0 (0.00%)	4 (6.90%)	1 (4.00%)	0 (0.00%)	3 (1.56%)	0 (0.00%)	0 (0.00%)	31 (5.84%)
6	1 (2.86%)	2 (2.11%)	10 (11.90%)	0 (0.00%)	0 (0.00%)	2 (3.45%)	2 (8.00%)	0 (0.00%)	31 (16.15%)	0 (0.00%)	0 (0.00%)	48 (9.04%)
mRS6m												287 (30.56%)
0	8 (23.53%)	20 (32.79%)	0 (0.00%)	7 (30.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	36 (22.36%)	0 (0.00%)	0 (0.00%)	71 (24.74%)
1	9 (26.47%)	15 (24.59%)	0 (0.00%)	6 (26.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	54 (33.54%)	0 (0.00%)	0 (0.00%)	84 (29.27%)
2	7 (20.59%)	13 (21.31%)	0 (0.00%)	4 (17.39%)	0 (0.00%)	3 (50.00%)	0 (0.00%)	0 (0.00%)	28 (17.39%)	0 (0.00%)	0 (0.00%)	55 (19.16%)
3	4 (11.76%)	5 (8.20%)	0 (0.00%)	3 (13.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (4.35%)	0 (0.00%)	0 (0.00%)	19 (6.62%)
4	4 (11.76%)	4 (6.56%)	0 (0.00%)	3 (13.04%)	0 (0.00%)	3 (50.00%)	0 (0.00%)	0 (0.00%)	2 (1.24%)	0 (0.00%)	0 (0.00%)	16 (5.57%)
5	1 (2.94%)	3 (4.92%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	1 (0.62%)	0 (0.00%)	0 (0.00%)	6 (2.09%)

Table 2 Continued

6	1 (2.94%)	1 (1.64%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	33 (20.50%)	0 (0.00%)	0 (0.00%)	36 (12.54%)
mRS1y												295 (31.42%)
0	0 (0.00%)	22 (38.60%)	10 (13.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (23.03%)	0 (0.00%)	0 (0.00%)	70 (23.73%)
1	0 (0.00%)	14 (24.56%)	24 (32.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	65 (39.39%)	0 (0.00%)	0 (0.00%)	103 (34.92%)
2	0 (0.00%)	13 (22.81%)	15 (20.55%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	17 (10.30%)	0 (0.00%)	0 (0.00%)	45 (15.25%)
3	0 (0.00%)	3 (5.26%)	8 (10.96%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	10 (6.06%)	0 (0.00%)	0 (0.00%)	21 (7.12%)
4	0 (0.00%)	4 (7.02%)	4 (5.48%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.61%)	0 (0.00%)	0 (0.00%)	9 (3.05%)
5	0 (0.00%)	0 (0.00%)	1 (1.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.61%)	0 (0.00%)	0 (0.00%)	2 (0.68%)
6	0 (0.00%)	1 (1.75%)	11 (15.07%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	33 (20.00%)	0 (0.00%)	0 (0.00%)	45 (15.25%)
GOS30d												251 (26.73%)
1	0 (0.00%)	0 (0.00%)	10 (16.67%)	0 (0.00%)	0 (0.00%)	14 (12.61%)	2 (5.26%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	26 (10.36)
2	0 (0.00%)	0 (0.00%)	1 (1.67%)	1 (2.38%)	0 (0.00%)	3 (2.70%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (1.99%)

Table 2 Continued

3	0 (0.00%)	0 (0.00%)	42 (70.00%)	6 (14.29%)	0 (0.00%)	13 (11.71%)	11 (28.95%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	72 (28.69%)
4	0 ()0.00%	0 (0.00%)	4 (6.67%)	8 (19.05%)	0 (0.00%)	35 (31.53%)	7 (18.42%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	54 (21.51%)
5	0 (0.00%)	0 (0.00%)	3 (5.00%)	27 (64.29%)	0 (0.00%)	46 (41.44%)	18 (47.37%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	94 (37.45%)
GOS3m												356 (37.91%)
1	0 (0.00%)	0 (0.00%)	10 (17.24%)	0 (0.00%)	0 (0.00%)	2 (3.45%)	2 (8.00%)	0 (0.00%)	31 (16.15%)	0 (0.00%)	0 (0.00%)	45 (12.64%)
2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.04%)	0 (0.00%)	0 (0.00%)	2 (0.56%)
3	0 (0.00%)	0 (0.00%)	28 (48.28%)	3 (13.04%)	0 (0.00%)	4 (6.90%)	5 (20.00%)	0 (0.00%)	11 (5.73%)	0 (0.00%)	0 (0.00%)	51 (14.33%)
4	0 (0.00%)	0 (0.00%)	9 (15.52%)	4 (17.39%)	0 (0.00%)	14 (24.14%)	8 (32.00%)	0 (0.00%)	55 (28.65%)	0 (0.00%)	0 (0.00%)	90 (25.28%)
5	0 (0.00%)	0 ()0.00%	11 (18.97%)	16 (69.57%)	0 (0.00%)	38 (65.52%)	10 (40.00%)	0 (0.00%)	93 (48.44%)	0 (0.00%)	0 (0.00%)	168 (47.19%)
GOS6m												364 (38.76%)
1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	15 (9.26%)	0 (0.00%)	1 (50.00%)	0 (0.00%)	33 (10.50%)	0 (0.00%)	0 (0.00%)	49 (13.46%)
2	2 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.55%)

Table 2 Continued

3	3 (9.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	19 (11.73%)	2 (33.33%)	1 (50.00%)	0 (0.00%)	3 (1.86%)	0 (0.00%)	0 (0.00%)	28 (7.69%)
4	6 (18.18%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	48 (29.63%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	39 (24.22%)	0 (0.00%)	0 (0.00%)	95 (26.10%)
5	22 (66.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	80 (49.38%)	2 (33.33%)	0 (0.00%)	0 (0.00%)	86 (53.42%)	0 (0.00%)	0 (0.00%)	190 (52.20%)
GOS1y												221 (23.54%)
1	0 (0.00%)	0 (0.00%)	10 (17.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	33 (20.00%)	0 (0.00%)	0 (0.00%)	43 (19.46%)
2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
3	0 (0.00%)	0 (0.00%)	10 (17.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.82%)	0 (0.00%)	0 (0.00%)	13 (5.88%)
4	0 (0.00%)	0 (0.00%)	8 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	33 (20.00%)	0 (0.00%)	0 (0.00%)	41 (18.55%)
5	0 (0.00%)	0 (0.00%)	28 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	96 (58.18%)	0 (0.00%)	0 (0.00%)	124 (56.11%)
DIND												566 (60.28%)
No	29 (78.38%)	73 (76.84%)	61 (70.93%)	35 (63.64%)	0 (0.00%)	2 (22.22%)	34 (77.27%)	0 (0.00%)	89 (45.35%)	0 (0.00%)	40 (83.33%)	363 (64.13%)
Yes	8 (21.62%)	22 (23.16%)	25 (29.07%)	20 (36.36%)	0 (0.00%)	7 (77.78%)	10 (22.73%)	0 (0.00%)	103 (53.65%)	0 (0.00%)	8 (16.67%)	203 (35.87%)

Table 2 continued

Rad_inf												107 (11.40%)
No	28 (75.68%)	80 (84.21%)	68 (85.00%)	38 (69.09%)	0 (0.00%)	0 (0.00%)	21 (47.73%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	61 (57.01%)
Yes	9 (24.32%)	15 (15.79%)	12 (15.00%)	17 (30.91%)	0 (0.00%)	0 (0.00%)	23 (52.27%)	26 (100.0%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	46 (42.99%)
Angio_VS												504 (53.67%)
No	0 (0.00%)	58 (61.05%)	22 (37.29%)	35 (63.64%)	0 (0.00%)	106 (79.70%)	1 (14.29%)	0 (0.00%)	60 (53.10%)	12 (54.55%)	13 (65.00%)	307 (60.91%)
Yes	0 (0.00%)	37 (38.95%)	37 (62.71%)	20 (36.36%)	0 (0.00%)	27 (20.30%)	6 (85.71%)	0 (0.00%)	53 (46.90%)	10 (45.45%)	7 (35.00%)	197 (39.09)
Def_VS												561 (59.74%)
No	31 (88.57%)	0 (0.00%)	0 (0.00%)	29 (70.73%)	64 (68.82%)	67 (50.38%)	39 (92.86%)	27 (79.41%)	87 (47.54%)	0 (0.00%)	0 (0.00%)	344 (61.32%)
Yes	4 (11.43%)	0 (0.00%)	0 (0.00%)	12 (29.27%)	28 (31.18%)	66 (49.62%)	3 (7.14%)	7 (20.59%)	96 (52.46%)	0 (0.00%)	0 (0.00%)	217 (38.68%)

3.1.3 Haptoglobin

Hardy-Weinberg equilibrium of each study was assessed, and the detailed result of frequency and percentage were shown in Table 3. The chi2 were calculated by OEGE online calculator, and p-values were calculated at 1 degree of freedom.

Table 3. Descriptive of Hp genotype

	Study A (n=37)	Study B (n=95)	Study C (n=86)	Study D (n=55)	Study E (n=169)	Study F (n=143)	Study G (n=46)	Study H (n=37)	Study I (n=192)	Study J (n=30)	Stud K (n=49)	All (n=939)
Hp1-1	8 (21.62%)	7 (7.37%)	11 (12.79%)	13 (23.64%)	25 (14.79%)	34 (23.78%)	15 (32.61%)	6 (16.22%)	25 (13.02%)	9 (30.00%)	7 (14.29%)	160 (17.04%)
Hp2-1	16 (43.24%)	39 (41.05%)	45 (52.33%)	30 (54.55%)	80 (47.34%)	62 (43.36%)	24 (52.17%)	22 (59.46%)	109 (56.77%)	10 (33.33%)	26 (53.06%)	463 (49.31%)
Hp2-2	13 (35.14%)	49 (51.58%)	30 (34.88%)	12 (21.82%)	64 (37.87%)	47 (32.87%)	7 (15.22%)	9 (24.32%)	58 (30.21%)	11 (36.67%)	16 (32.65%)	316 (33.65%)
Chi-2	0.52	0.04	0.86	0.46	0	2.26	0.27	1.44	5.55	3.27	0.47	0.19
p-value	0.471	0.841	0.354	0.498	1	0.133	0.603	0.230	0.018	0.071	0.493	0.663

From Table 3 Hp in most studies had p-value larger than 0.05, which indicated they followed Hardy-Weinberg equilibrium and didn't have ascertainment bias. However, in study I, the chi2 was 5.55 with p-value 0.018, which is much smaller than 0.05, and we can conclude that there was significant difference between observed and expected data. This bias may be caused by some other influences, such as gender, race, and something else. However, these are independent samples and the subjects are not related biologically.

3.2 TWO-STAGE ANALYSIS

The odds ratio was assessed, both unadjusted and adjusted. The unadjusted analysis calculated the odds ratio of clinical outcome between different groups of Hp without controlling any other covariates except time. The adjusted analysis was assessed while controlling core covariates and same additional covariates.

The primary outcome was unfavorable outcome, defined as mRS 3-6 or GOS 1-3 when mRS were not available. All included 8 studies with primary outcome measure were mRS except for Study E with only GOS measure. Logistic regression model was used for Study E given only 6 months measurement. Meta-Analysis of pooled odds ratio were calculated in STATA software (version 14.0 SE StataCorp, College Station, TX).

3.2.1 Primary outcome (mRS and GOS)

The point estimation, confidence interval and p-value of odds ratio are shown in Table 4 and 5, respectively.

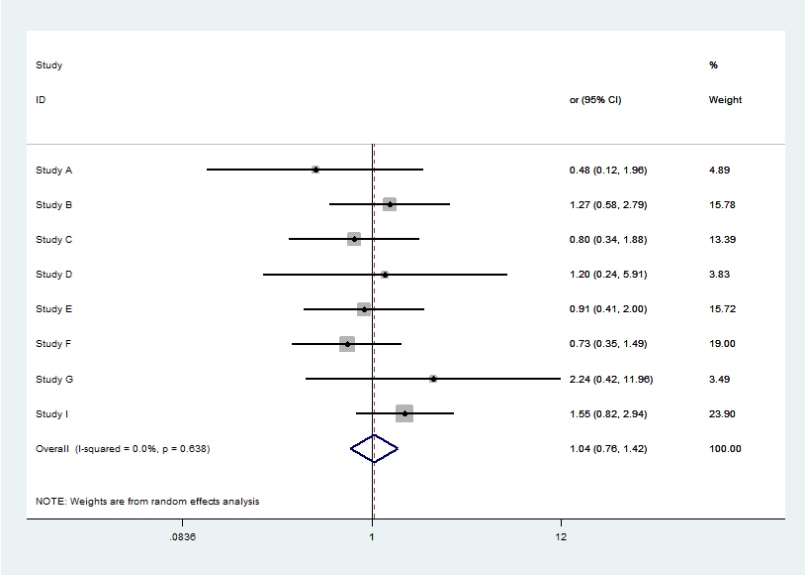
Table 4. The univariate association between Hp_variant (22 vs 11 & 21) and unfavorable outcome using GEE adjusting for time

Study ID	Sample size	Time point	OR	95% CI	P-value
A	37	3,6	0.478	(0.116,1.963)	0.306
B	95	1,3,6	1.267	(0.577,2.785)	0.555
C	86	1,3	0.799	(0.340,1.878)	0.607
D	55	1,3,6	1.195	(0.242,5.914)	0.827

Table 4 Continued

E	169	6	0.909	(0.413, 2.00)	0.813
F	143	1,3	0.725	(0.354,1.486)	0.380
G	46	1,3	2.244	(0.421,11.959)	0.344
I	192	3,6	1.549	(0.817,2.936)	0.180
Meta-Analysis	Pooled	1,3,6	1.035	(0.757,1.415)	0.828

Table 4 above compared primary outcome in rare homozygotes (Hp-22) versus common homozygotes (Hp-11) and heterozygotes (Hp-21). From the Table 4, without adjusting any other covariates except time, all results were not significant, and we could conclude that there is no significant association between Hp and primary outcomes in any study group. Meta-analysis was used to assess the pooled odds ratio, and Figure 1 showed the result.

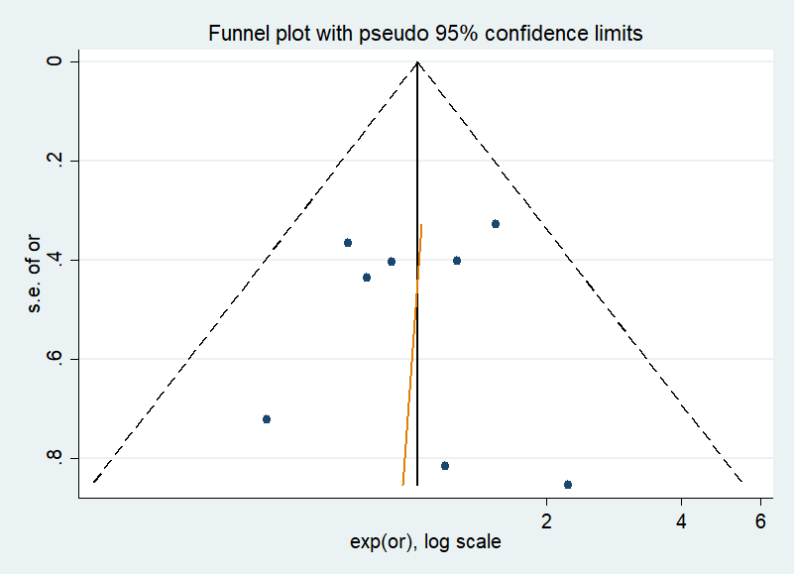


- Heterogeneity chi-squared=5.18 (df=7) p=0.638
- I-squared =0.0%
- Estimate of between-study variance Tau-squared=0.0000

- **Figure 1.** The pooled univariate association between Hp_variant (22 vs 11 & 21) and unfavorable outcome adjusting for time

Meta-analysis of overall odds ratio indicated there were no significant difference between rare homozygotes versus common homozygotes and heterozygotes for primary outcomes, while

not controlling other covariates except time. The p-value of Q test indicated there was no significant heterogeneity (p=0.638) and I^2 indicated no heterogeneity was observed (I^2=0.00%).



- Bias: t=-0.18 p=0.866

Figure 2. Funnel plot of univariate association between Hp_variant (22 vs 11 & 21) and unfavorable outcome

Figure 2 did not have asymmetry problems, which indicated there was no publication bias in this analysis. In the Egger test, no bias was observed with p-value larger than 0.05 (p=0.866).

The adjusted analysis was calculated while controlling other covariates, and the covariates used are shown in Tables below.

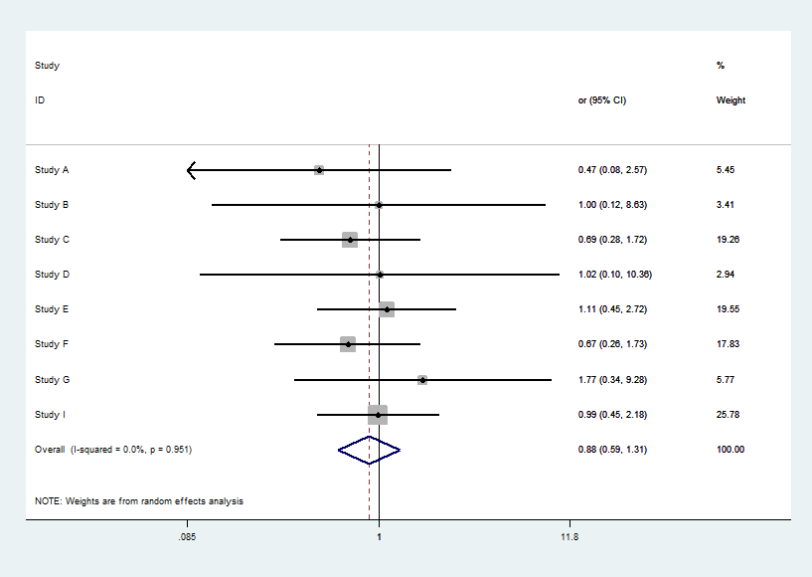
Table 5. The adjusted association between Hp_variant (22 vs 21 & 11) and unfavorable outcome using GEE

Study ID	covariate	Sample size	Time point	OR	95% CI	P-value
A	time HTN aneurysm treatment age WFNS fisher	37	3,6	0.467	（0.085,2.571）	0.382
B	time HTN aneurysm treatment age WFNS	95	1,3,6	1.001	(0.116,8.628)	0.999
C	time HTN aneurysm treatment age WFNS fisher	85	1,3	0.695	(0.281,1.723)	0.433
D	time HTN aneurysm treatment age WFNS fisher	42	1,3,6	1.017	(0.100,10.363)	0.988

Table 5 Continued

E	time HTN aneurysm treatment age WFNS fisher	161	6	1.106	(0.450,2.722)	0.826
F	time HTN aneurysm treatment age WFNS fisher	111	1,3	0.672	(0.262,1.725)	0.409
G	time HTN aneurysm treatment age WFNS	41	1,3	1.770	(0.338,9.279)	0.499
I	time HTN aneurysm treatment age WFNS fisher	183	3,6	0.994	(0.454,2.177)	0.988
Meta-Analysis		Pooled	1,3,6	0.877	(0.589,1.306)	0.519

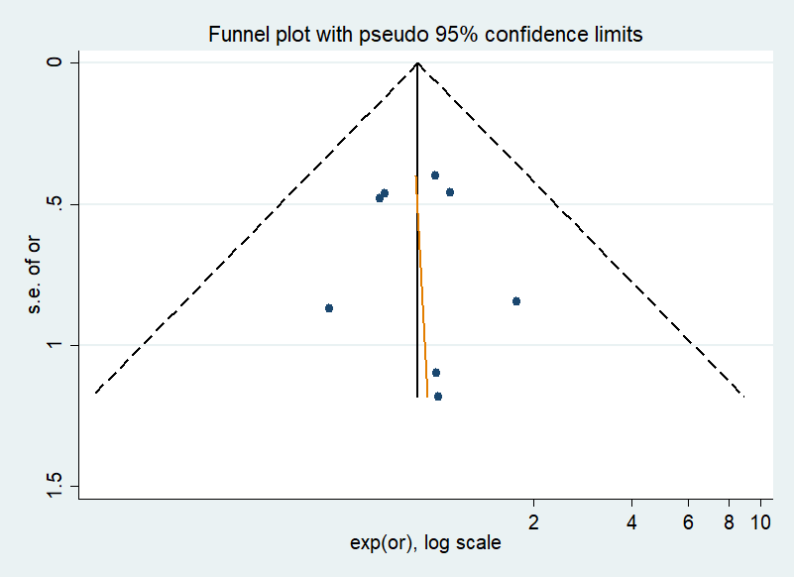
Table 5 showed the point estimate, confidence interval and p-value of the association between Hp-22 versus Hp-11 and Hp-21. In analysis of all studies, covariates including time, HTN, aneurysm, treatment, age and WFNS were controlled. In Studies A, C, D, E, F, and I, Fisher Grade were also controlled in the GEE models. In Study B and G, because of the highly skewed distribution of Fisher Grade which leads to an un-estimable model, the Fisher Grade was not included in analysis of these studies. The results showed no significant association between Hp_variants and unfavorable outcome. The Figure of overall results for the Meta-Analyses follows.



- Heterogeneity Chi-squared=2.16 (df=7) p=0.951
- I-squared = 0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 3. The pooled adjusted association between Hp_variant (22 vs 21 & 11) and unfavorable outcome

Figure 3 above indicated there was no significant association between Hp_variant and unfavorable outcome while adjusting some other covariates, which is same as the conclusion of the analysis without controlling other covariates except time. Q test and I^2 indicated there was no heterogeneity observed (p=0.951, I^2=0.0%)



- Bias: t=0.18 p=0.865

Figure 4. Funnel plot of adjusted association between Hp_variant (22 vs 11 & 21) and unfavorable outcome

In Figure 4, the outer dashed lines indicate the triangular region within which 95% of studies were expected to lie in the absence of both biases and heterogeneity, and the solid vertical line corresponds to no intervention effect. This plot is symmetric, which indicates that there was no publication bias. The Egger test indicated there was no small-study effects, hence, that there was no publication bias problem.

3.2.2 Sensitivity Analysis

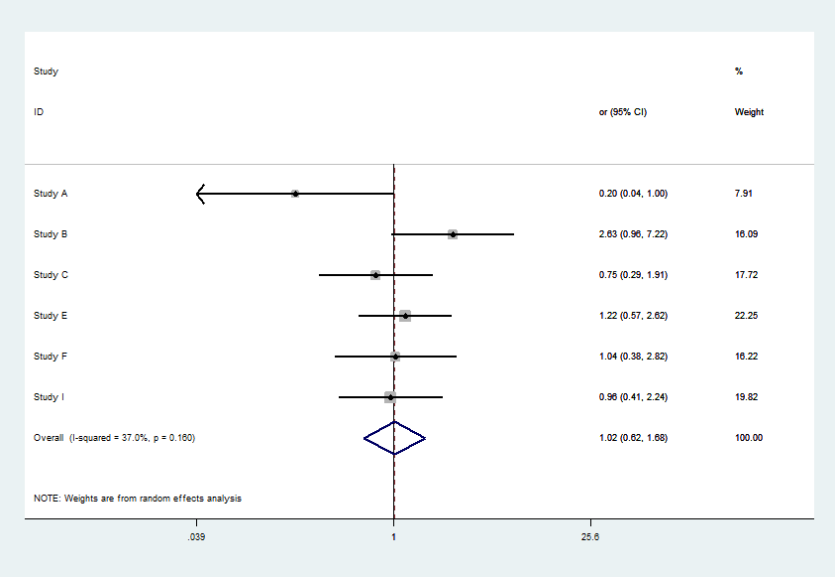
- **Sliding Dichotomy**

The primary outcomes were ordinal outcomes, and sliding dichotomy was based on mRS and GOS. This study included Study A, B, C, D, E, F, G, and I, and covariates including age, treatment, WFNS, HTN, and fisher grade were used to adjust the result. We included 8 studies with primary outcome measure (mRS) and one study, Study E, with only GOS measure.

Table 6. The association between Hp_variant (22 vs 21 & 11) and unfavorable outcome using sliding dichotomy

Study ID	Sample size	covariates	Time point	OR	95% CI	P-value
A	37	treatment age fisher wfns	3,6	0.198	(0.039,1.005)	0.051
B	95	treatment age wfns	1,3,6	2.633	(0.960,7.223)	0.060
C	86	age treatment fisher wfns	1,3	0.748	(0.294,1.907)	0.544
D	43	age treatment fisher wfns	1,3,6	empty		
E	161	age treatment fisher wifns	6	1.219	(0.568,2.619)	0.611
F	127	age treatment fisher wifns	1,3	1.036	(0.380,2.824)	0.945
G	42	age treatment wifns	1,3	empty		
I	192	age treatment fisher wifns	3,6	0.957	(0.409,2.241)	0.920
Meta-Analysis			pooled	1.017	(0.616,1.681)	0.946

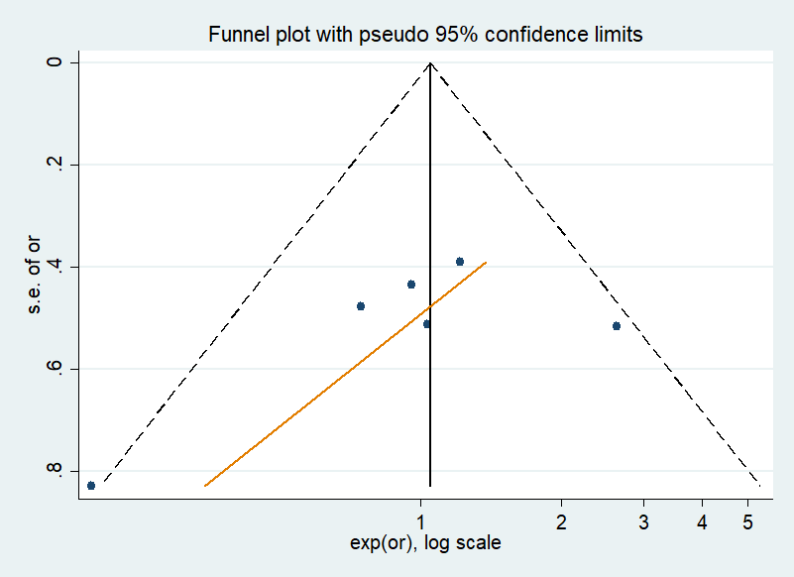
The odds ratio in Study D and G was not estimable by sliding dichotomy, and they were not included in further analysis. Table 6 indicated there was no effect of Hp variant was observed on unfavorable outcome.



- Heterogeneity Chi-squared = 1.94 (df=6) p=0.160
- I-squared=37%
- Estimate of between-study variance Tau-squared=0.1431

Figure 5. The pooled association between Hp_variant (22 vs 21 & 11) and unfavorable outcome using sliding dichotomy

Figure 5 above indicated the pooled sliding dichotomy odds ratio was not significant different from 1, and there was no significant association between Hp variant and mRS or GOS in meta-analysis. The Q test indicated no heterogeneity problem (p=0.160), and the I^2 showed 37% of the variability across studies was due to heterogeneity rather than chance. Although no significant heterogeneity was detected in Q test, the inconsistency was moderately large.



- Bias: t-1.37 p=0.243

Figure 6. Funnel plot of association between Hp_variant (22 vs 11 & 21) and unfavorable outcome using sliding dichotomy

In Figure 6, the funnel plot was symmetric, which indicates that there was no publication bias issue. The Egger test also concluded the funnel plot didn't have asymmetric issue and there was no publication bias.

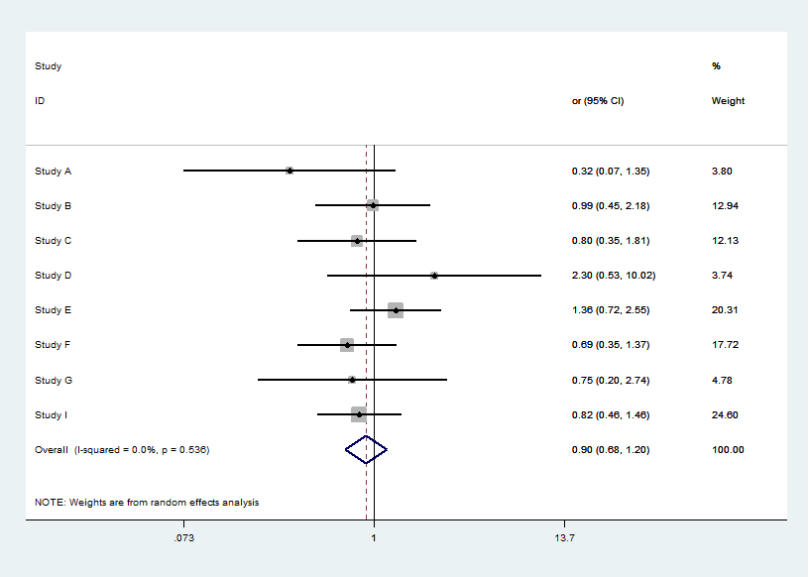
- **Proportional Odds Logistic Regression Model**

The primary outcome mRS and GOS are ordinal outcomes. Proportional odds logistic regression model was used to estimate the odds ratio for each of the possible cut points of the mRS and GOS. Study A, B, C, D, E, F, G, and I with primary outcome (mRS or GOS) were included in this analysis, controlling for time, HTN, treatment, age, fisher grade, and WFNS. We included 8 studies with primary outcome measure (mRS) and one study, Study E, with only GOS measure.

Table 7. The association between Hp_variant (22 vs 11 & 21) and unfavorable outcome using proportional odds logistic regression model

Study ID	covariate	Sample size	Time point	OR	95% CI	P-value
A	time HTN treatment age fisher WFNS	37	3,6	0.315	(0.073,1.354)	0.120
B	Time HTN treatment age WFNS	95	1,3,6	0.988	(0.448,2.181)	0.976
C	time HTN treatment age fisher WFNS	86	1,3	0.799	(0.353,1.810)	0.591
D	time HTN treatment age fisher WFNS	55	1,3,6	2.298	(0.527,10.020)	0.268
E	HTN treatment age fisher WFNS	169	6	1.356	(0.721,2.550)	0.345
F	time HTN treatment age fisher WFNS	143	1,3	0.694	(0.353,1.365)	0.290
G	time HTN treatment age WFNS	46	1,3	0.746	(0.203,2.744)	0.659
I	time HTN treatment age fisher WFNS	192	3,6	0.823	(0.464,1.462)	0.507
Meta-Analysis			pooled	0.899	(0.676,1.195)	0.464

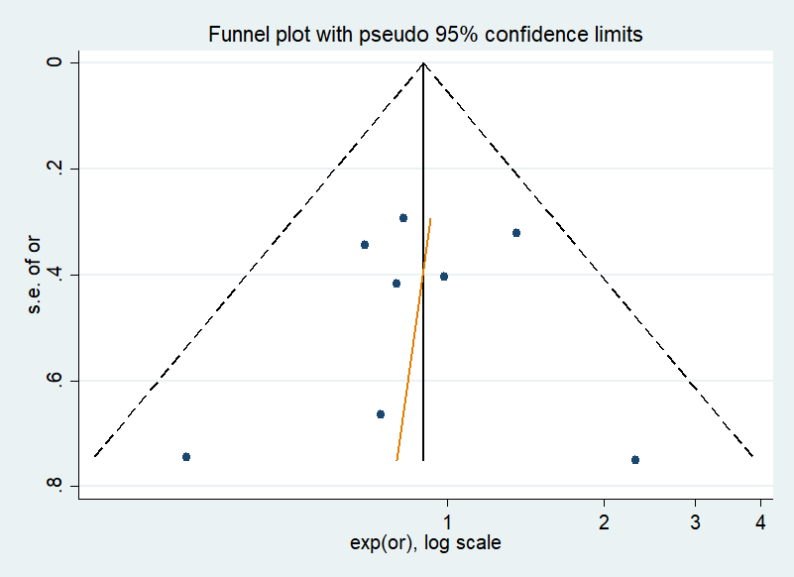
Table 7 above indicated there was no significant difference between the effect of different Hp variant (22 vs 11 & 21) on unfavorable outcome.



- Heterogeneity Chi-squared=6.04 (df=7) p=0.536
- I-squared =0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 7. The pooled association between Hp_variant (22 vs 11 & 21) and unfavorable outcome using proportional odds logistic regression model

Figure 7 above showed the common odds ratio using proportional odds logistic model as not significant different from 1, which indicated there was no significant effect of Hp variant on unfavorable outcome. In the heterogeneity test, both Q test and result of I^2 indicated no heterogeneity was observed.



- Bias: t=-0.30 p=0.775

Figure 8. Funnel plot of association between Hp_variant (22 vs 11 & 21) and unfavorable outcome using proportional odds logistic regression model

Figure 8 and the t-statistics of Egger test indicated there was no publication bias in this meta-analysis because the funnel plot was not asymmetric (p=0.775).

3.2.3 Secondary Outcome (DIND, Rad_inf, Angio_VS and Def_VS)

Secondary outcomes including DIND, Rad_inf (radiographic evidence of infarction), Angio_VS (Angiographic evidence of vasospasm), Def_VS (definite vasospasm/TCD evidence of vasospasm) were binary outcomes. Logistic regression models were conducted to look at connections between Hp genotype and outcomes. Models for the secondary outcomes were adjusted and unadjusted.

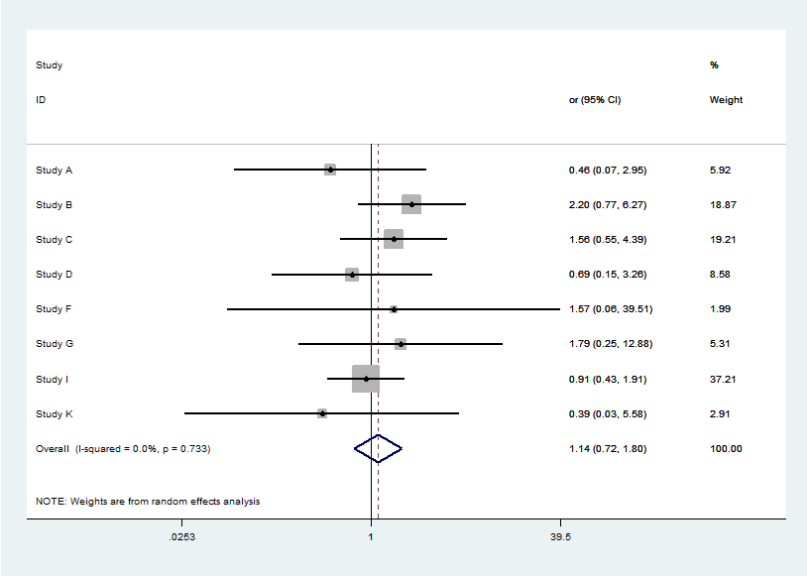
- **DIND**

Study A, B, C, D, G, and I contained information for DIND, and the analysis was based on these studies.

Table 8. The univariate association between Hp_variant (22 vs 11 & 21) and DIND

Study ID	Sample size	OR	95% CI	P-value
A	37	0.545	(0.093,3.194)	0.501
B	95	2.458	(0.897,6.736)	0.080
C	86	1.367	(0.522,3.578)	0.525
D	55	0.844	(0.219,3.255)	0.805
G	44	1.45	(0.236,8.923)	0.689
I	192	1.335	(0.716,2.488)	0.364
Meta-analysis		1.258	(0.686,2.308)	0.458

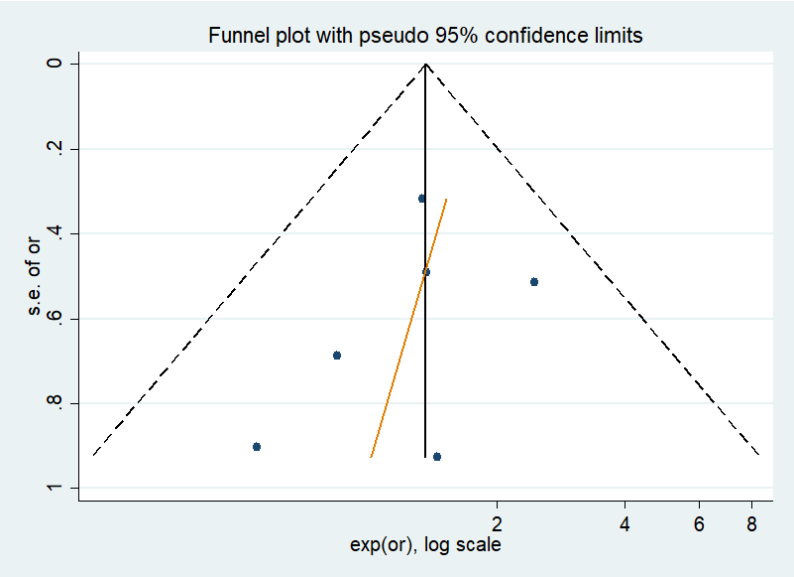
Table 8 indicated there were no significant association between Hp_variant (22 vs 11 & 21) and DIND outcome with all p-value larger than 0.05 in all studies.



- Heterogeneity Chi-squared=2.30 (df=5) p=0.806
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 9. The pooled univariate association between Hp_variant (22 vs 11 & 21) and DIND

The result of Meta-Analysis above in Figure 9 indicated no effect of Hp_variant on DIND was observed (p-value=0.145). Q test indicated there was no heterogeneity problem, and I^2 showed the same conclusion.



- Bias: t=-0.77 t=0.485

Figure 10. Funnel plot of univariate association between Hp_variant (22 vs 11 & 21) and DIND

Figure 10 was symmetric which indicated there was no publication bias problem. The p-value of bias in Egger test was 0.485 which confirmed the conclusion from the plot.

The adjusted logistic regression model was used, and the result was as follows.

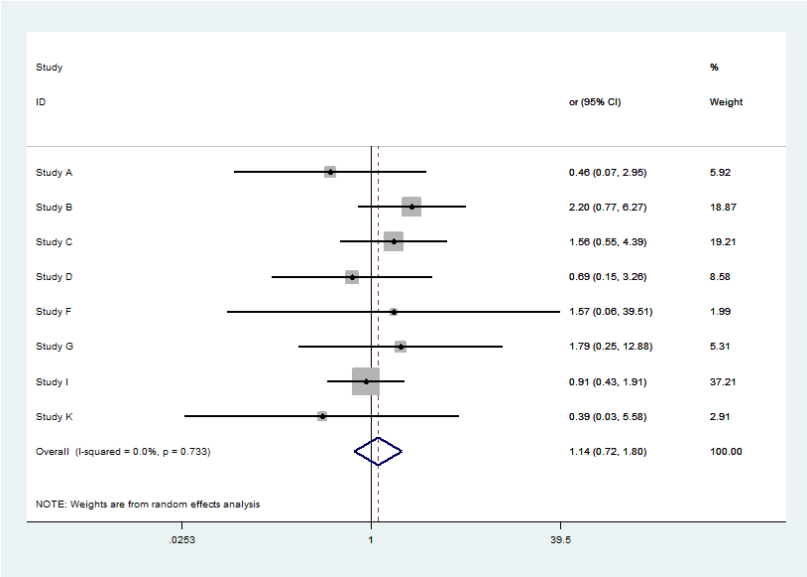
Table 9. The adjusted association between Hp_variant (22 vs 11 & 21) and DIND

Study ID	covariates	Sample size	OR	95% CI	P-value
A	Age WFNS Treatment HTN	37	0.455	(0.070,2.947)	0.409
B	Age WFNS Treatment HTN	95	2.201	(0.772,6.274)	0.140
C	Age WFNS Treatment HTN	84	1.556	(0.551,4.395)	0.404
D	Age WFNS Treatment HTN Fisher	55	0.690	(0.146,3.263)	0.640
F	Age	9	1.566	(0.062,39.515)	0.786
G	Age WFNS Treatment HTN	43	1.788	(0.248,12.884)	0.564

Table 9 Continued

I	Age WFNS Treatment HTN Fisher	183	0.907	(0.430,1.912)	0.797
K	Age Treatment HTN Fisher	24	0.393	(0.027,5.584)	0.490
Meta-Analysis			1.141	(0.724,1.798)	0.571

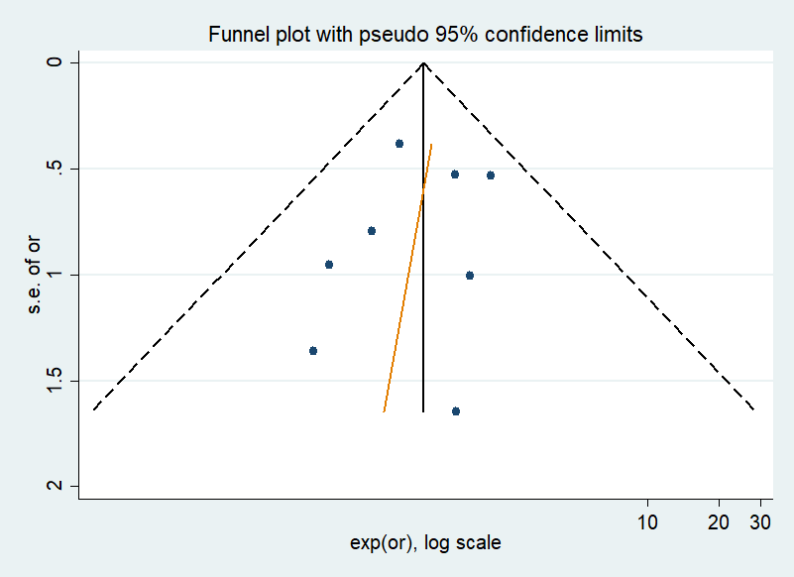
Table 9 indicated there was no effect of Hp variant (22 vs 11 & 21) on DIND outcome while controlling for other covariates, including age, WFNS, treatment, HTN, and fisher grade. For Study F, only age was the only covariate being adjusted.



- Heterogeneity Chi-squared=4.40 (df=7) p=0.733
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 11. The pooled adjusted association between Hp_variant (22 vs 11 & 21) and DIND

Figure 11 indicated the odds ratio from the pooled logistic regression analysis on Hp variant and DIND outcome was not significant different from 1, which indicated DIND didn't change in different Hp variant. Both Q test in I^2 indicated no heterogeneity issue in this meta-analysis and the result was consistent.



- Bias: t=-0.53 p=0.618

Figure 12. Funnel plot of adjusted association between Hp_variant (22 vs 11 & 21) and DIND

Figure 12 didn't show asymmetric and there was no publication bias issue. In the test of asymmetric in funnel plot, Egger test showed there was asymmetric issue which indicated no small-study effects was observed.

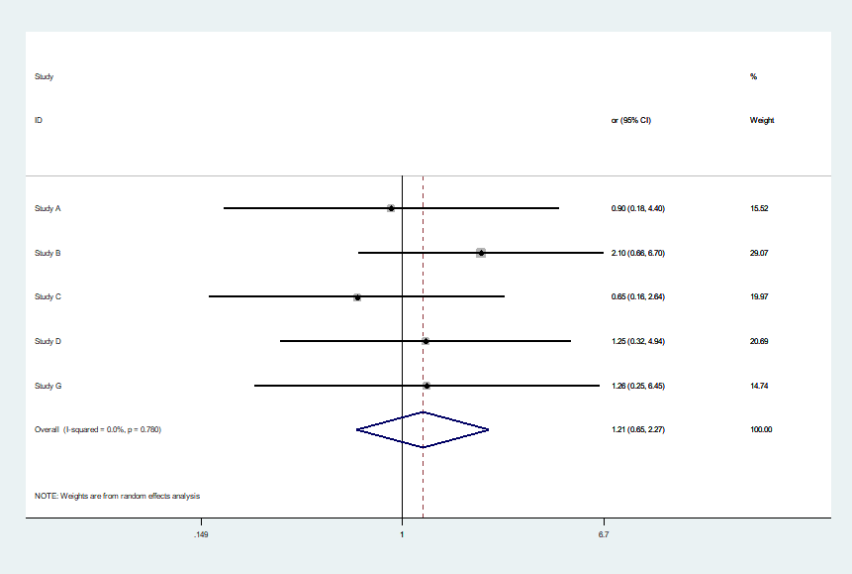
- **Rad_inf**

Study A, B, C, D, and G had information of Rad_inf, and they were included in this analysis.

Table 10. The univariate association between Hp_variant (22 vs 11 & 21) and Rad_inf

Study ID	Sample size	OR	95% CI	P-value
A	37	0.900	(0.184,4.400)	0.896
B	95	2.103	(0.659,6.704)	0.209
C	80	0.652	(0.161,2.644)	0.550
D	54	1.25	(0316,4.940)	0.750
G	44	1.26	(0.248,6.446)	0.779
Meta-Analysis		1.215	(0.650,2.270)	0.542

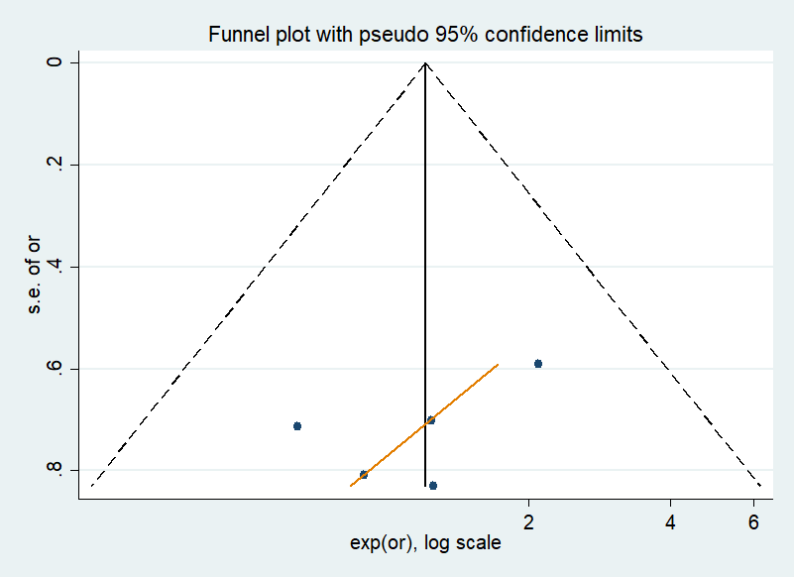
Table 10 above indicated no significant effect of Hp variant (22 vs 11 & 21) on Rad_inf outcome was observed.



- Heterogeneity Chi-squared=1.76 (df=4) p=0.780
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 13. The pooled univariate association between Hp_variant (22 vs 11 & 21) and Rad_inf

Figure 13 showed the pooled odds ratio of Rad_inf in Hp-22 versus Hp-11 and Hp-21. The result indicated there was not significant association between Hp_variant and Rad_inf. Large p-value of Q test (p=0.780) and value of I^2 indicated no heterogeneity was observed in this study.



- Bias: t=-1.39 p=0.259

Figure 14. Funnel plot of univariate association between Hp_variant (22 vs 11 & 21) and Rad_inf

Plot in Figure 14 looked symmetric, and Egger test didn't show asymmetric issue, which indicated was no publication bias problem.

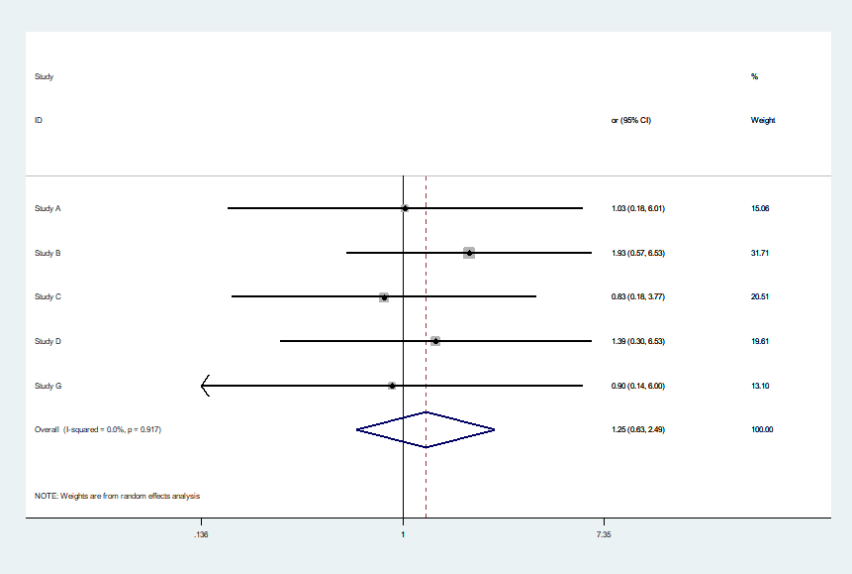
The results while controlling other covariates follows.

Table 11. The adjusted association between Hp_variant (22 vs 11 & 21) and Rad_inf

Study ID	Covariate	Sample size	OR	95% CI	P-value
A	Aneurysm Age WFNS Treatment HTN	37	1.027	(0.176,6.013)	0.976
B	Aneurysm Age WFNS Treatment HTN	95	1.934	(0.573,6.533)	0.288
C	Aneurysm Age WFNS Treatment HTN	79	0.832	(0.183,3.773)	0.812
D	Aneurysm Age WFNS Treatment HTN Fisher	54	1.390	(0.296,6.535)	0.677
G	Aneurysm Age WFNS Treatment HTN Fisher	43	0.905	(0.136,5.999)	0.917
Meta_Analysis			1.255	(0.632,2.490)	0.516

After controlling other covariates (aneurysm, age, WFNS, treatment, HTN, and fisher grade in some studies), as Table 11 showed above, the point estimate was different, but p-value

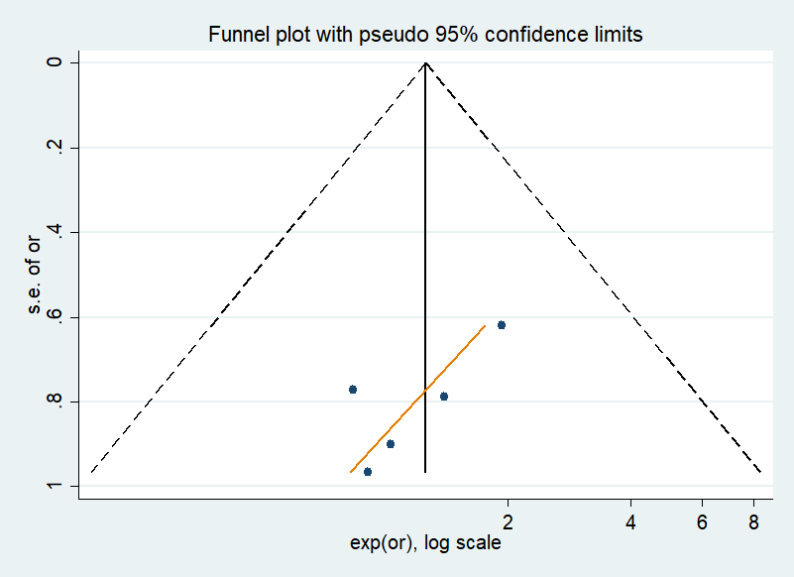
are all larger than 0.05, indicating there was no significant association between Hp_variant (22 vs 11 & 21) and Rad_inf.



- Heterogeneity Chi-squared=0.95 (df=4) p=0.917
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 15. The pooled adjusted association between Hp_variant (22 vs 11 & 21) and Rad_inf

Figure 15 indicated there was no effect of Hp_variant (22 vs 11 & 21) on Rad_inf was observed while controlling other covariates. In the test of heterogeneity, both Q test and I^2 indicated there was no heterogeneity, and the result of analysis was consistent.



- Bias: t=-2.2 p=0.115

Figure 16. Funnel plot of adjusted association between Hp_variant (22 vs 11 & 21) and Rad_inf

Figure 16 indicated the two-stage adjusted analysis of association between Hp genotype and Rad_inf didn't have publication bias (p=0.115).

The adjusted analysis had different result from unadjusted one after controlling for other covariates. However, they all had the same conclusion that Hp variant did not have a significant effect on Rad_inf outcome.

- **Def_VS**

Analysis of Def_VS was based on Study A, D, E, F, G, H, and I. This analysis consisted two parts: unadjusted and adjusted. The results were as following.

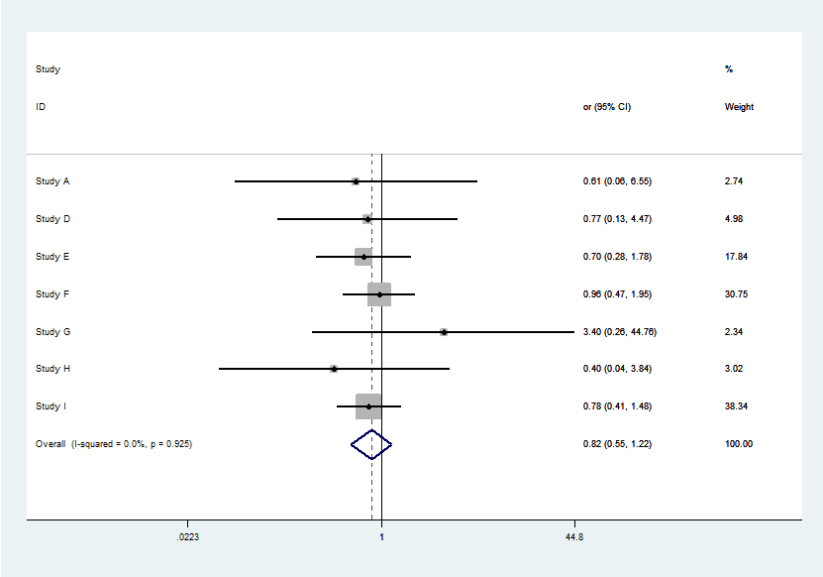
Table 12. The univariate association between Hp_variant (22 vs 11 & 21) and Def_VS

Study ID	Sample size	OR	95% CI	P-value
A	35	0.606	(0.056,6.547)	0.680
D	41	0.767	(0.131,4.475)	0.768
E	93	0.702	(0.276,1.785)	0.457
F	133	0.958	(0.471,1.952)	0.907

Table 12 Continued

G	42	3.4	(0.258,44.758)	0.352
H	34	0.396	(0.041,3.841)	0.424
I	183	0.783	(0.414,1.479)	0.450
Meta-Analysis		0.822	(0.554,1.219)	0.329

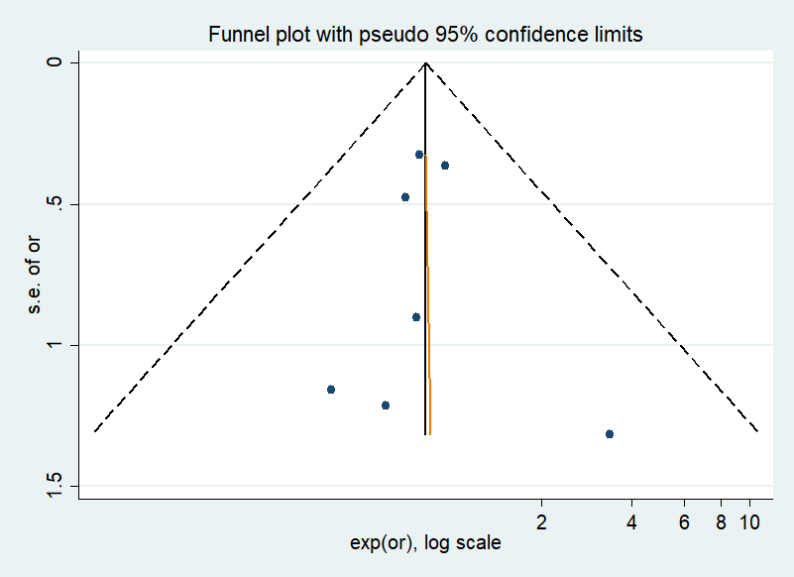
Table 12 above indicated there were no significant association between Hp_variant (22 vs 11 & 21) and Def_VS with p-value in all studies were larger than 0.05.



- Heterogeneity Chi-squared-1.94 (df=6) p=0.925
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 17. The pooled univariate association between Hp_variant (22 vs 11 & 21) and Def_VS

Figure 17 indicated the univariate association between Hp_variant and Def_VS was not significant, and the pooled odds ratio was close to 1 (p-value=0.329). Q test and I^2 indicated no variability between studies that cannot be explained by chance (I^2=0.0%).



- Bias: t=0.08 p=0.936

Figure 18. Funnel plot of univariate association between Hp_variant (22 vs 11 & 21) and Def_VS

Figure 18 and test statistic of Egger test indicated there was no publication bias since the plot was symmetric (p=0.936).

The adjusted analysis of Def_VS was also done in these studies. However, controlling for all covariates in the modelling had problems including no convergence. In most studies, we controlled for age, WFNS, treatment, and fisher grade, but for Study A we only adjusted for HTN and age, for Study G we only adjusted for age, HTN and WFNS, and for Study H we controlled for age only.

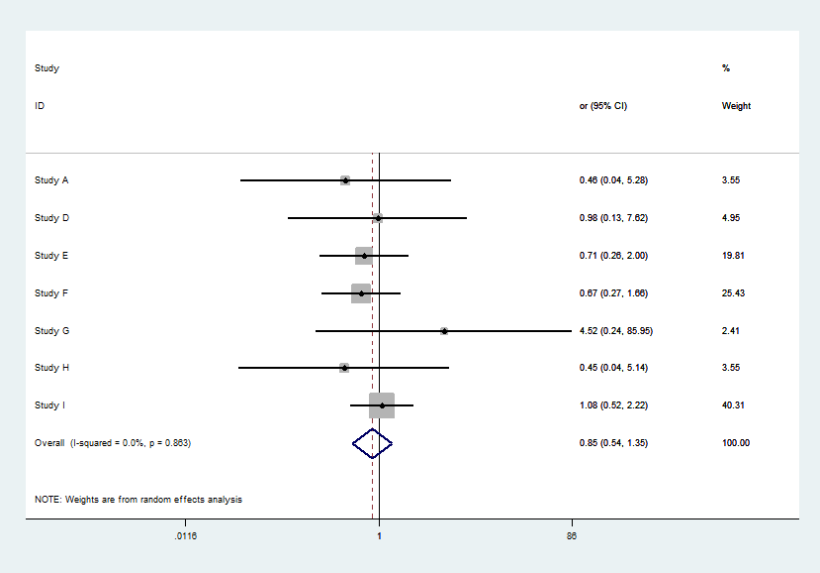
Table 13. The adjusted association between Hp_variant (22 vs 11 & 21) and Def_VS

Study ID	Covariate	Sample size	OR	95% CI	P-value
A	HTN Age	35	0.463	(0.041,5.279)	0.535
D	Age WFNS Treatment HTN Fisher	41	0.978	(0.125,7.619)	0.983
E	Age WFNS Treatment HTN Fisher	93	0.715	(0.256,2.000)	0.523
F	Age WFNS Treatment HT Fisher	116	0.669	(0.270,1.657)	0.385
G	Age HTN WFNS	41	4.518	(0.237,85.951)	0.316

Table 13 Continued

H	Age	34	0.454	(0.040,5.139)	0.524
I	Age WFNS Treatment HT Fisher	174	1.079	(0.525,2.218)	0.836
Meta-Analysis			0.854	(0.540,1.349)	0.498

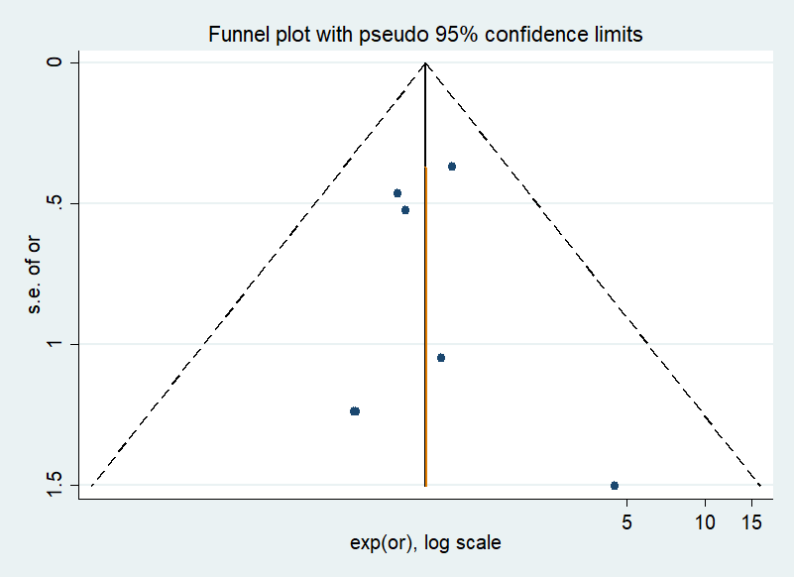
Table 13 above indicated there were no significant effect of Hp variant on Def_VS outcome with p-value in all group were larger than 0.05. The range of 95% confidence interval in Study G was quite wide (0.237, 85.951), so further analysis with more observation was needed.



- Heterogeneity Chi-squared=2.55 (df=6) p=0.863
- I-squared=0.0%
- Estimate of between-study variance Tau-squared=0.0000

Figure 19. The pooled adjusted association between Hp_variant (22 vs 11 & 21) and Def_VS

In the result of Meta-analysis in Figure 19, Study I had the heaviest weight, and the conclusion was no significant association between Hp_variant and Def_VS at level 0.05. Both Q test and I^2 indicated chance could explain all variability between studies as p-value larger than 0.05 and 0.0% I^2.



- Bias: t=0.01 p=0.995

Figure 20. Funnel plot of adjusted association between Hp_variant (22 vs 11 & 21) and Def_VS

Plot in Figure 20 indicated there was no publication bias since no asymmetric issue was observed (p=0.995).

The conclusion of adjusted analysis was same as unadjusted one, even though they had different results.

- **Angio_VS**

The analysis on Angio_VS outcome was based on Study B, C, D, F, I, J, and K. The sample size of Study J and K were quite small. The unadjusted and adjusted were used in this analysis, and the results were as follows.

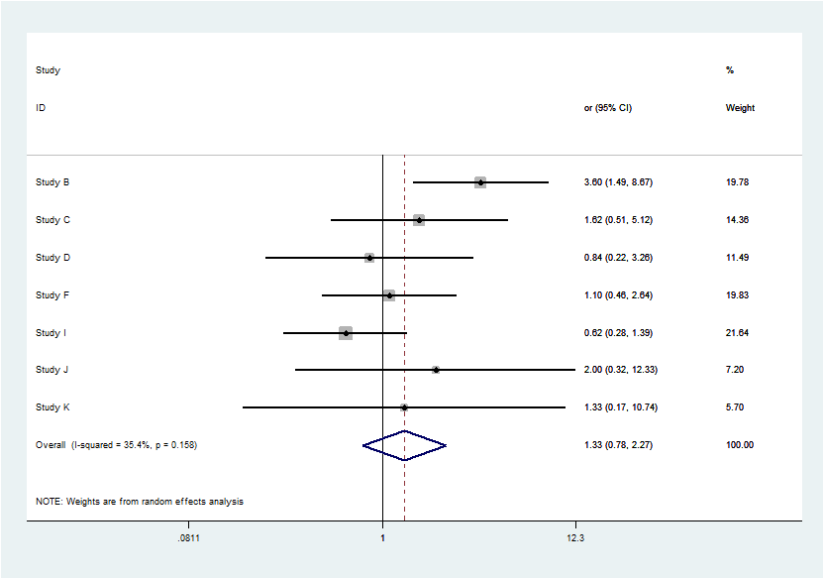
Table 14. The univariate association between Hp_variant (22 vs 11 & 21) and Angio_VS

Study ID	Sample size	OR	95% CI	P-value
B	95	3.597	(1.492,8.668)	0.004
C	59	1.623	(0.514,5.125)	0.409
D	55	0.844	(0.219,3.255)	0.805

Table 14 Continued

F	133	1.097	(0.456,2.638)	0.836
I	113	0.620	(0.277,1.387)	0.245
J	22	2	(0.324,12.329)	0.455
K	20	1.333	(0.165,10.743)	0.787
Meta-Anlysis		1.329	(0.778,2.271)	0.298

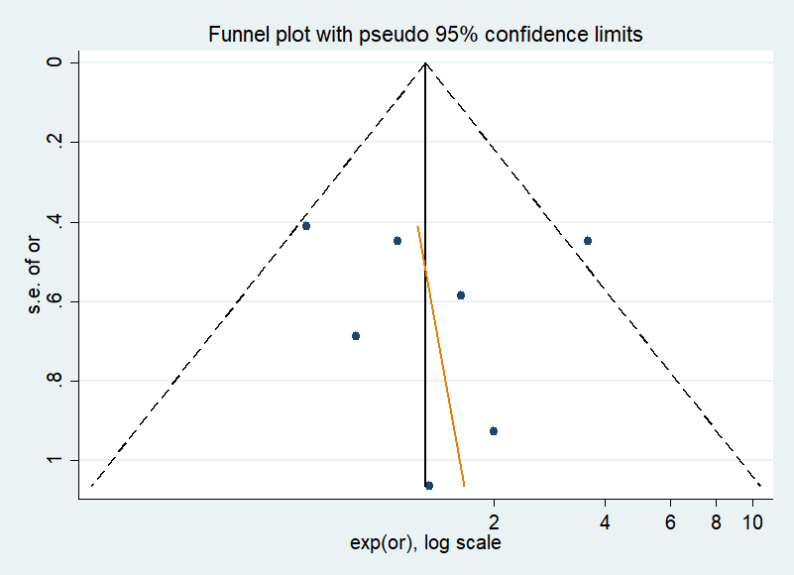
Table 14 above showed the unadjusted association between Hp_variant and Angio_VS outcome. Most p-value were larger than 0.05, and the null hypothesis that there was no association was not rejected in any study. However, the p-value of Study B was less than 0.05, which indicated Hp-22 genotype imparted a better Angio_VS outcome compared to Hp-11 and Hp-21 (OR=3.597, 95% CI (1.492,8.668), p=0.004).



- Heterogeneity Chi-squared=9.28 (df=6) p=0.158
- I-squared=35.4%
- Estimate of between-study variance Tau-squared=0.1767

Figure 21. The pooled univariate association between Hp_variant (22 vs 11 &21) and Angio_VS

Although the odds ratio of Study B was larger than 1, the pooled odds ratio from Figure 21 was still not significantly different from 1, which indicated there was not association between Hp_variant and Angio_VS outcome. In the test of heterogeneity, Q test indicated the heterogeneity is not significant, but I^2 is 35.4% and it was moderately large.



- Bias: t=0.26 p=0.804

Figure 22. Funnel plot of univariate association between Hp_variant (22 vs 11 & 21) and Angio_VS

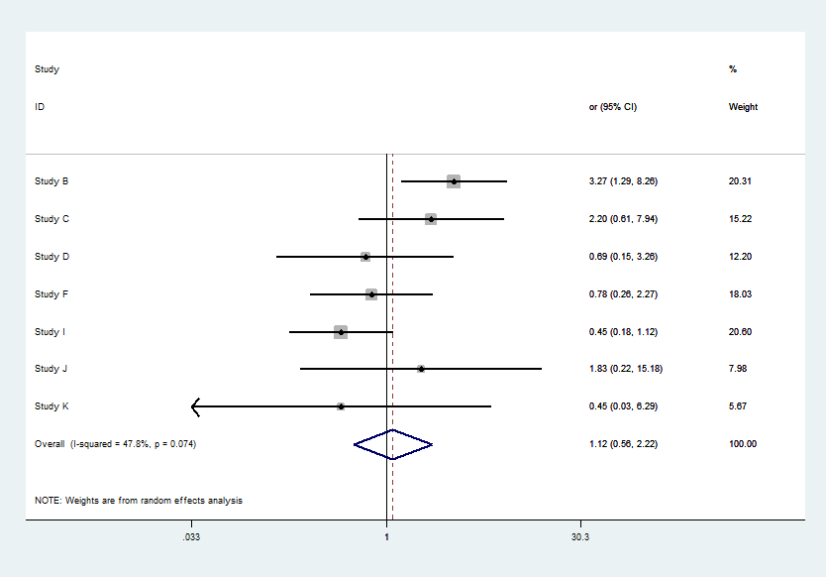
Although there was one outlier in funnel plot in Figure 22, there were no publication bias issue since the plot was symmetric (p=0.804).

In the adjusted analysis, covariates including age, WFNS, treatment, HTN and fisher grade were used except study I and K.

Table 15. The adjusted association between Hp_variant (22 vs 11 & 21) and Angio_VS

Study ID	Covariate	Sample size	OR	95% CI	P-value
B	Age WFNS Treatment HTN Fisher	94	3.268	(1.293,8.262)	0.012
C	Age WFNS Treatment HTN Fisher	59	2.203	(0.612,7.936)	0.227
D	Age WFNS Treatment HTN Fisher	55	0.690	(0.146,3.263)	0.640
F	Age WFNS Treatment HTN Fisher	116	0.776	(0.265,2.273)	0.643
I	Age WFNS Treatment HTN Fisher	107	0.452	(0.182,1.122)	0.087
J	Age Treatment HTN	22	1.834	(0.221,15.176)	0.574
K	Age Treatment HTN	20	0.453	(0.033,6.294)	0.556
Meta-Analysis			1.125	(0.707,1.791)	0.619

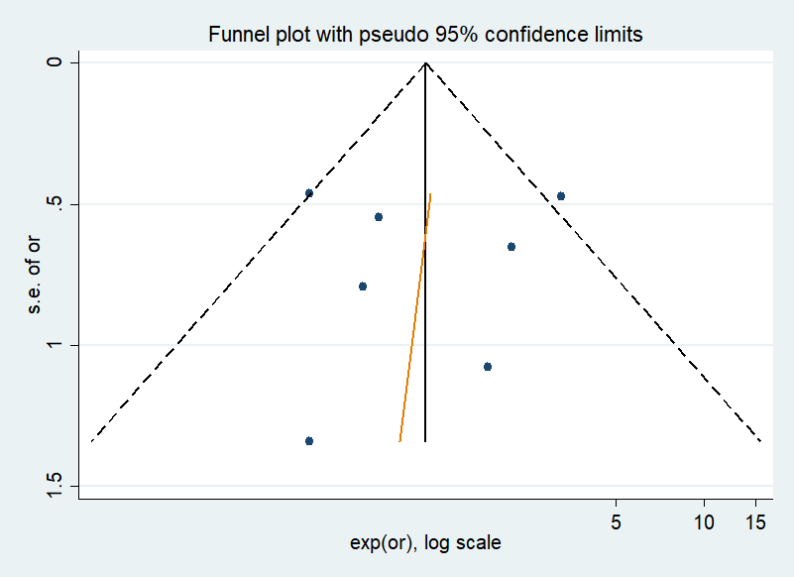
In Table 15, after controlling for covariates, Hp-22 genotype in Study B still had significant higher probability to have Angio_VS (p=0.012).



- Heterogeneity Chi-squared=11.50 (df=6) p=0.074
- I-squared=47.8%
- Estimate of between-study variance Tau-squared=0.3844

Figure 23. The pooled adjusted association between Hp_variant (22 vs 11 &21) and Angio_VS

From Figure 23 above, although the odds ratio of Study B was significantly different from 1, the pooled effect of Hp variant on Angio_VS was not observed. There is no significant heterogeneity in Q test (p=0.074), but I^2 showed that majority of the variability across studies were because of heterogeneity, and the inconsistency was moderately large (I^2=47.8%)



- Bias: t=-0.16 p=0.882

Figure 24. Funnel plot of adjusted association between Hp_variant (22 vs 11 & 21) and Angio_VS

There was one outlier in Figure 24 which needed to be considered, but the plot is symmetric and there was no publication bias (p=0.882).

3.3 ONE-STAGE ANALYSIS

One-stage analysis was used for both primary and secondary outcomes. In the primary outcome, study site and time were considered as random effect. In the secondary outcome, study site was considered as random effect. The comparison of result in two-stage and one-stage analysis is as following.

Table 16. The univariate association between Hp_variant (22 vs 21 & 11) and outcome summary

Outcome	Two-Stage (OR 95% CI p-value)	One-Stage (OR 95% CI p-value)
mRS & GOS	1.035 (0.757,1.415) 0.828	1.322 (0.443,3.964) 0.617
DIND	1.361 (0.889,2.061) 0.145	1.305 (0.887,1.920) 0.177
Rad_inf	1.215 (0.650,2.270) 0.542	1.193 (0.656,2.171) 0.563
Angio_VS	1.304 (0.886,1.964) 0.203	1.297 (0.874,1.923) 0.196
Def_VS	0.822 (0.554,1.219) 0.329	0.822 (0.556,1.216) 0.327

Table 16 above indicated the result of univariate association in two-stage and one-stage analysis in primary outcome had some difference but the results for secondary outcome were quite similar with each other. The difference in primary outcome may because of different methods. The GEE method was used in first step of two-stage analysis, and mixed effect logistic model was used in one-stage analysis. Both analyses had the same conclusion of no pooled effect of Hp on outcome after aSAH was observed.

Table 17. The adjusted association between Hp_variant (22 vs 21 & 11) and outcome summary

Outcome	covariates	Two-Stage (OR 95% CI p-value)	One-Stage (OR 95% CI p-value)
mRS&GOS	Age WFNS Treatment Time	0.877 (0.589,1.306) 0.519	1.180 (0.387,3.601) 0.771
DIND	Age WFNS HTN Treatment	1.141 (0.724,1.798) 0.571	1.324 (0.872,2.010) 0.199
Rad_inf	Age WFNS HTN Treatment	1.225 (0.632,2.490) 0.516	1.110 (0.604,2.043) 0.736
Angio_VS	Age WFNS HTN Treatment	1.125 (0.707,1.791) 0.619	1.249 (0.811,1.923) 0.312
Def_VS	Age WFNS HTN Treatment	0.854 (0.540,1.349) 0.498	0.901 (0.583,1.392) 0.638

In Table 17, the difference between two-stage and one-stage analysis while controlling for other covariates was more than unadjusted analysis, which may be caused by the covariates being used in the adjusted models. Meanwhile, these two analyses drew the same conclusion that there was no significant association between Hp variant and outcome.

4.0 DISCUSSION AND CONCLUSION

Individual level Meta-analyses on the inconsistent findings from the current literature for the association between Hp and aSAH recovering are lacking, and most previous research focused on one outcome.

The primary outcomes (mRS and GOS) were measured repeatedly up to 6 months. The outcome measure of the same subject at different time points are correlated, hence GEE method with logistic regression model was used to account for the correlation between different time measurements within the same subject. The odds ratio in each study and the pooled odds ratio across all studies, which were obtained from meta-analysis, indicated there was no association between Hp genotype and unfavorable outcome.

Secondary outcome analysis was a cross sectional study based on four different outcomes. Without the effect of time on each subject, logistic regression model was used in each outcome of each study. Although in some studies different Hp genotype had different effect on some outcomes, the pooled odds ratio still indicated no relationship between Hp and secondary outcomes.

Sliding dichotomy and proportional odds logistic regression are two alternative models to avoid losing information about outcome and reducing statistical power of mRS and GOS. Using these two models in an ordinal outcome is more accurate and precise rather than simply

dichotomizing. The Meta-analysis still indicated there was no pooled association between Hp genotype and unfavorable outcome.

In the two-stage analysis, logistic regression model was used in the first step to estimate the odds ratio in each study on both primary and secondary outcomes. The GEE method was conducted for primary outcomes because of the repeated measurements. With different effect sizes, a meta-analysis with random effect model was conducted in the second step. For some outcomes in the first step analysis, the odds ratio and p-value indicated there was an effect of Hp genotype on outcome, but there was no significant association after combing all studies by meta-analysis. In the test of heterogeneity in meta-analysis, all studies showed there was no heterogeneity in Q test, but I^2 in some studies indicated majority of the variability across studies were due to heterogeneity instead of chance, and the inconsistency was moderately large. Large I^2 in these studies may be due to lack of power with a small number of studies (less than 10 studies). The I^2 estimate's dependence on power, trial weights and time-lag bias, and these factors may cause fluctuation beyond the play of chance. Reporting 95% confidence interval should be more appropriate to assess the degree of heterogeneity. The funnel plot was used to access the publication bias in meta-analysis, and all plots were symmetric and there was no publication bias. Also, Egger test generated the same conclusion that all funnel didn't have asymmetric problem.

In one-stage analysis, all data were fitted in mixed effect logistic regression model, and each study was considered as a cluster. For primary outcomes, each individual subject was also considered as a cluster because of repeated measurement over time. Results for the secondary outcome analysis was quite similar as the two-stage analysis, but there were some differences between two approaches for the primary outcome. There are few reasons for this difference.

Firstly, the GEE method was used in first step of the two-stage analysis, but the one-stage analysis used a mixed model, different methods with different equations may lead to different results. Second, each study had a different weight in the meta-analysis and the mixed model, which is another reason for this difference.

In the analyses of Hp and primary outcome at each time point, there were some significant associations between Hp and aSAH in some studies, but the pooled odds ratio from meta-analysis still indicated a negative relationship.

The sample size in each study was relatively small, and the subjects were mainly white/caucasian. This limits the generalization of the results. The Hp genotype/allele frequencies in Study I weren't in Hardy-Weinberg equilibrium. Interactions of covariates in this study could be considered in the model to have a more accurate estimation. GOS and mRS are long-term outcome measures after aSAH, so extending study period with more time points will provide a more appropriate estimate. Analyzing some other, more detailed outcomes of aSAH recovery is another way to assess the relationship between Hp genotype and aSAH.

In summary negative findings were ascertained for the association between Hp genotype and outcome after aSAH from meta-analysis. However, given the limited number and small sample size of the studies included, the association needs to be evaluated further with more large-scaled prospective studies.

APPENDIX A: RELEVANT STATA CODES (mRS)

```
Import excel "D:\pitt\study\Project-Meta\part 2\IPLD_coded_combined_ANALYSIS_pitt_08011
7 (1).xlsx", sheet("Data") firstrow allstring clear
*transfer mRS to two results, 1 for favorable, 0 for unfavorable
gen m1=.
replace m1=0 if mRS30d=="0"
replace m1=0 if mRS30d=="1"
replace m1=0 if mRS30d=="2"
replace m1=1 if mRS30d=="3"
replace m1=1 if mRS30d=="4"
replace m1=1 if mRS30d=="5"
replace m1=1 if mRS30d=="6"
gen m2=.
replace m2=0 if mRS3m=="0"
replace m2=0 if mRS3m=="1"
replace m2=0 if mRS3m=="2"
replace m2=1 if mRS3m=="3"
replace m2=1 if mRS3m=="4"
replace m2=1 if mRS3m=="5"
```

```
replace m2=1 if mRS3m=="6"
gen m3=.
replace m3=0 if mRS6m=="0"
replace m3=0 if mRS6m=="1"
replace m3=0 if mRS6m=="2"
replace m3=1 if mRS6m=="3"
replace m3=1 if mRS6m=="4"
replace m3=1 if mRS6m=="5"
replace m3=1 if mRS6m=="6"



*generate obs for data
gen obs=_n

*transfer data from wide to long (longitudinal)
reshape long m, i(obs) j(time)



*transfer time as 1, 3, 6 months (time2 as core covariate)
gen time2=.
replace time2=1 if time==1
replace time2=3 if time==2
replace time2=6 if time==3
```

```
*transfer Age, Treatment, WFNS, Fisher, Hp from string to numeric data
destring Age, gen(age)
destring Treatment, gen(treatment)
destring WFNS, gen(wfns)
destring Fisher, gen(fisher)
gen hpp=.
replace hpp=0 if Hp=="1"
replace hpp=0 if Hp=="2"
replace hpp=1 if Hp=="3"

*don't analysis 6 month in Study F and G
drop if Study_ID=="F" & time2==6
drop if Study_ID=="G" & time2==6
drop if treatment==3

*mRS unadjusted
xtgee m i.hpp i.time if Study_ID =="A"&(time2==3|time2==6), family(b) link(logit) corr(exch)
i(obs) t(time2) robust eform
xtgee m i.hpp i.time if Study_ID =="B", family(b) link(logit) corr(exch) i(obs) t(time2) robust
eform
xtgee m i.hpp i.time if Study_ID =="C"&(time2==1|time2==3), family(b) link(logit) corr(exch)
i(obs) t(time2) robust eform
```

```
xtgee m i.hpp i.time if Study_ID =="D", family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
xtgee m i.hpp i.time if Study_ID =="F"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
xtgee m i.hpp i.time if Study_ID =="G"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
xtgee m i.hpp i.time if Study_ID =="I"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform

*change treatment and do GEE with covariates
gen treatment1=.
replace treatment1=1 if treatment==1
replace treatment1=2 if treatment==2
gen diabetes=.
replace diabetes=1 if Diabetes=="1"
replace diabetes=0 if Diabetes=="0"
destring HTN,gen( htn )
destring Aneurysm,gen(aneurysm)
destring Race, gen(race)

gen a1=.
replace a1=0 if aneurysm ==1
replace a1=0 if aneurysm ==2
```

replace a1=0 if aneurysm ==3

replace a1=1 if aneurysm ==4

xtgee m i.hpp i.time htn i.treatment1 age i.wfns i.fisher if Study_ID =="A"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns if Study_ID =="B", family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns i.fisher if Study_ID =="C"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns i.fisher if Study_ID =="D", family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns i.fisher if Study_ID =="F"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns if Study_ID =="G"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

xtgee m i.hpp i.time htn i.treatment1 age i.wfns i.fisher if Study_ID =="I"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform nolog

**sliding dichotomy

**study A

xtgee m i.time i.treatment1 i.a1 i.htn age i.fisher i.wfns if Study_ID =="A"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform

predict phatA if Study_ID=="A" & (time2==3|time2==6)

xtile phata=phatA, nquantiles(3)

gen dichotomy=.

replace dichotomy=1 if Study_ID=="A"&(time2==3|time2==6)&(m==1|m==0)

replace dichotomy=0 if mRS3m=="0" & Study_ID=="A" & time2==3

replace dichotomy=0 if mRS3m=="1" & Study_ID=="A" & time2==3

replace dichotomy=0 if mRS3m=="2" & Study_ID=="A" & time2==3

replace dichotomy=0 if mRS3m=="3" & Study_ID=="A" & time2==3 &(phata==2|phata==3)

replace dichotomy=0 if mRS3m=="4" & Study_ID=="A" & time2==3 &phata==3

replace dichotomy=0 if mRS6m=="0" & Study_ID=="A" & time2==6

replace dichotomy=0 if mRS6m=="1" & Study_ID=="A" & time2==6

replace dichotomy=0 if mRS6m=="2" & Study_ID=="A" & time2==6

replace dichotomy=0 if mRS6m=="3" & Study_ID=="A" & time2==6 &(phata==2|phata==3)

replace dichotomy=0 if mRS6m=="4" & Study_ID=="A" & time2==6 &phata==3

****study A in overall

xtgee dichotomy i.hpp time i.treatment1 age i.fisher i.wfns if Study_ID =="A"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform

**Study B

xtgee m i.time diabetes htn a1 i.treatment1 age i.wfns if Study_ID =="B", family(b) link(logit) corr(exch) i(obs) t(time2) robust eform

predict phatB if Study_ID=="B"

```
xtile phatb=phatB, nquantiles(3)
replace dichotomy=1 if Study_ID=="B"&(m==1|m==0)
replace dichotomy=0 if mRS3m=="0" & Study_ID=="B" & time2==3
replace dichotomy=0 if mRS3m=="1" & Study_ID=="B" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="B" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="B" & time2==3 &(phatb==2|phatb==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="B" & time2==3 &phatb==3
replace dichotomy=0 if mRS6m=="0" & Study_ID=="B" & time2==6
replace dichotomy=0 if mRS6m=="1" & Study_ID=="B" & time2==6
replace dichotomy=0 if mRS6m=="2" & Study_ID=="B" & time2==6
replace dichotomy=0 if mRS6m=="3" & Study_ID=="B" & time2==6 &(phatb==2|phatb==3)
replace dichotomy=0 if mRS6m=="4" & Study_ID=="B" & time2==6 &phatb==3
replace dichotomy=0 if mRS30d=="0" & Study_ID=="B" & time2==1
replace dichotomy=0 if mRS30d=="1" & Study_ID=="B" & time2==1
replace dichotomy=0 if mRS30d=="2" & Study_ID=="B" & time2==1
replace dichotomy=0 if mRS30d=="3" & Study_ID=="B" & time2==1 &(phatb==2|phatb==3)
replace dichotomy=0 if mRS30d=="4" & Study_ID=="B" & time2==1 &phatb==3
****study B overall
xtgee dichotomy i.hpp i.time i.treatment1 age i.wfns if Study_ID =="B", family(b) link(logit)
corr(exch) i(obs) t(time2) robust eform
**study C
xtgee m i.time diabetes htn a1 age i.treatment1 i.fisher i.wfns if Study_ID
=="C"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
```

```
predict phatC if Study_ID=="C" & (time2==1|time2==3)
xtile phatc=phatC, nquantiles(3)
replace dichotomy=1 if Study_ID=="C"&(time2==3|time2==1)&(m==1|m==0)
replace dichotomy=0 if mRS30d=="0" & Study_ID=="C" & time2==1
replace dichotomy=0 if mRS30d=="1" & Study_ID=="C" & time2==1
replace dichotomy=0 if mRS30d=="2" & Study_ID=="C" & time2==1
replace dichotomy=0 if mRS30d=="3" & Study_ID=="C" & time2==1 &(phatc==2|phatc==3)
replace dichotomy=0 if mRS30d=="4" & Study_ID=="C" & time2==1 &phatc==3
replace dichotomy=0 if mRS3m=="0" & Study_ID=="C" & time2==3
replace dichotomy=0 if mRS3m=="1" & Study_ID=="C" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="C" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="C" & time2==3 &(phatc==2|phatc==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="C" & time2==3 &phatc==3
***study C overall
xtgee dichotomy i.hpp i.time age i.treatment1 i.fisher i.wfns if Study_ID
=="C"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
**Study D
xtgee m i.time diabetes htn i.treatment1 age i.fisher i.wfns if Study_ID =="D", family(b)
link(logit) corr(exch) i(obs) t(time2) robust eform
predict phatD if Study_ID=="D"
xtile phatd=phatD, nquantiles(3)
replace dichotomy=1 if Study_ID=="D"&(m==1|m==0)
replace dichotomy=0 if mRS3m=="0" & Study_ID=="D" & time2==3
```

```
replace dichotomy=0 if mRS3m=="1" & Study_ID=="D" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="D" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="D" & time2==3 &(phatd==2|phatd==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="D" & time2==3 &phatd==3
replace dichotomy=0 if mRS6m=="0" & Study_ID=="D" & time2==6
replace dichotomy=0 if mRS6m=="1" & Study_ID=="D" & time2==6
replace dichotomy=0 if mRS6m=="2" & Study_ID=="D" & time2==6
replace dichotomy=0 if mRS6m=="3" & Study_ID=="D" & time2==6 &(phatd==2|phatd==3)
replace dichotomy=0 if mRS6m=="4" & Study_ID=="D" & time2==6 &phatd==3
replace dichotomy=0 if mRS30d=="0" & Study_ID=="D" & time2==1
replace dichotomy=0 if mRS30d=="1" & Study_ID=="D" & time2==1
replace dichotomy=0 if mRS30d=="2" & Study_ID=="D" & time2==1
replace dichotomy=0 if mRS30d=="3" & Study_ID=="D" & time2==1 &(phatd==2|phatd==3)
replace dichotomy=0 if mRS30d=="4" & Study_ID=="D" & time2==1 &phatd==3
***study D overall
xtgee dichotomy i.hpp i.time i.treatment1 age i.fisher i.wfns if Study_ID =="D", family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
**Study F
xtgee m i.time diabetes htn a1 age i.treatment1 i.fisher i.wfns if Study_ID =="F"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
predict phatF if Study_ID=="F" & (time2==1|time2==3)
xtile phatf=phatF, nquantiles(3)
replace dichotomy=1 if Study_ID=="F"&(time2==3|time2==1)&(m==1|m==0)
```

```
replace dichotomy=0 if mRS30d=="0" & Study_ID=="F" & time2==1
replace dichotomy=0 if mRS30d=="1" & Study_ID=="F" & time2==1
replace dichotomy=0 if mRS30d=="2" & Study_ID=="F" & time2==1
replace dichotomy=0 if mRS30d=="3" & Study_ID=="F" & time2==1 &(phatf==2|phatf==3)
replace dichotomy=0 if mRS30d=="4" & Study_ID=="F" & time2==1 &phatf==3
replace dichotomy=0 if mRS3m=="0" & Study_ID=="F" & time2==3
replace dichotomy=0 if mRS3m=="1" & Study_ID=="F" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="F" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="F" & time2==3 &(phatf==2|phatf==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="F" & time2==3 &phatf==3
**study F overall
xtgee dichotomy i.hpp i.time htn age i.treatment1 i.fisher i.wfns if Study_ID =="F"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
**study G
xtgee m i.time diabetes htn a1 i.treatment1 age i.wfns if Study_ID =="G"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
predict phatG if Study_ID=="G" & (time2==1|time2==3)
xtile phatg=phatG, nquantiles(3)
replace dichotomy=1 if Study_ID=="G"&(time2==3|time2==1)&(m==1|m==0)
replace dichotomy=0 if mRS30d=="0" & Study_ID=="G" & time2==1
replace dichotomy=0 if mRS30d=="1" & Study_ID=="G" & time2==1
replace dichotomy=0 if mRS30d=="2" & Study_ID=="G" & time2==1
replace dichotomy=0 if mRS30d=="3" & Study_ID=="G" & time2==1 &(phatg==2|phatg==3)
```

```
replace dichotomy=0 if mRS30d=="4" & Study_ID=="G" & time2==1 &phatg==3
replace dichotomy=0 if mRS3m=="0" & Study_ID=="G" & time2==3
replace dichotomy=0 if mRS3m=="1" & Study_ID=="G" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="G" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="G" & time2==3 &(phatg==2|phatg==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="G" & time2==3 &phatg==3
**study G overall
xtgee dichotomy i.hpp i.time i.treatment1 htn age i.wfns if Study_ID =="G"&(time2==1|time2==3), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
**study I
xtgee m i.time diabetes htn a1 age i.treatment1 i.fisher i.wfns if Study_ID =="I"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform
predict phatI if Study_ID=="I" & (time2==3|time2==6)
xtile phati=phatI, nquantiles(3)
replace dichotomy=1 if Study_ID=="I"&(time2==3|time2==6)&(m==1|m==0)
replace dichotomy=0 if mRS3m=="0" & Study_ID=="I" & time2==3
replace dichotomy=0 if mRS3m=="1" & Study_ID=="I" & time2==3
replace dichotomy=0 if mRS3m=="2" & Study_ID=="I" & time2==3
replace dichotomy=0 if mRS3m=="3" & Study_ID=="I" & time2==3 &(phati==2|phati==3)
replace dichotomy=0 if mRS3m=="4" & Study_ID=="I" & time2==3 &phati==3
replace dichotomy=0 if mRS6m=="0" & Study_ID=="I" & time2==6
replace dichotomy=0 if mRS6m=="1" & Study_ID=="I" & time2==6
replace dichotomy=0 if mRS6m=="2" & Study_ID=="I" & time2==6
```

replace dichotomy=0 if mRS6m=="3" & Study_ID=="I" & time2==6 &(phati==2|phati==3)

replace dichotomy=0 if mRS6m=="4" & Study_ID=="I" & time2==6 &phati==3

**study I overall

xtgee dichotomy i.hpp i.time htn age i.treatment1 i.fisher i.wfns if Study_ID =="I"&(time2==3|time2==6), family(b) link(logit) corr(exch) i(obs) t(time2) robust eform

**oridinal

***prepare

gen om=.

replace om=4 if mRS30d=="4" & time2==1

replace om=4 if mRS30d=="5" & time2==1

replace om=4 if mRS30d=="6" & time2==1

replace om=3 if mRS30d=="3" & time2==1

replace om=2 if mRS30d=="2" & time2==1

replace om=1 if mRS30d=="1" & time2==1

replace om=0 if mRS30d=="0" & time2==1

replace om=4 if mRS3m=="4" & time2==3

replace om=4 if mRS3m=="5" & time2==3

replace om=4 if mRS3m=="6" & time2==3

replace om=3 if mRS3m=="3" & time2==3

replace om=2 if mRS3m=="2" & time2==3

replace om=1 if mRS3m=="1" & time2==3

replace om=0 if mRS3m=="0" & time2==3

replace om=4 if mRS6m=="4" & time2==6

replace om=4 if mRS6m=="5" & time2==6

replace om=4 if mRS6m=="6" & time2==6

replace om=3 if mRS6m=="3" & time2==6

replace om=2 if mRS6m=="2" & time2==6

replace om=1 if mRS6m=="1" & time2==6

replace om=0 if mRS6m=="0" & time2==6

**study A

ologit om i.hpp i.time htn i.treatment1 age i.fisher i.wfns if Study_ID =="A"&(time2==3|time2==6), cluster(obs) or

**study B

ologit om i.hpp i.time htn i.treatment1 age i.wfns if Study_ID =="B",cluster(obs) or

**study C

ologit om i.hpp i.time htn age i.treatment1 i.fisher i.wfns if Study_ID =="C"&(time2==1|time2==3),cluster(obs) or

**study D

ologit om i.hpp i.time htn i.treatment1 age i.fisher i.wfns if Study_ID =="D",cluster(obs) or

**study F

ologit om i.hpp i.time htn i.treatment1 age i.fisher i.wfns if Study_ID =="F"&(time2==1|time2==3),cluster(obs) or

**study G

ologit om i.hpp i.time htn i.treatment1 age i.wfns if Study_ID =="G"&(time2==1|time2==3),cluster(obs) or

**study I

ologit om i.hpp i.time htn i.treatment1 age i.fisher i.wfns if Study_ID =="I"&(time2==3|time2==6),cluster(obs) or

APPENDIX B: RELEVANT STATA CODES (GOS)

```
import excel "D:\pitt\study\Project-Meta\part 2\IPLD_coded_combined_ANALYSIS_pitt_080117 (1).xlsx", sheet("Data") firstrow allstring clear

gen g1=.
replace g1=0 if GOS30d=="4"
replace g1=0 if GOS30d=="5"
replace g1=1 if GOS30d=="1"
replace g1=1 if GOS30d=="2"
replace g1=1 if GOS30d=="3"
gen g2=.
replace g2=0 if GOS3m=="4"
replace g2=0 if GOS3m=="5"
replace g2=1 if GOS3m=="1"
replace g2=1 if GOS3m=="2"
replace g2=1 if GOS3m=="3"
gen g3=.
replace g3=0 if GOS6m=="4"
replace g3=0 if GOS6m=="5"
```

```
replace g3=1 if GOS6m=="1"
replace g3=1 if GOS6m=="2"
replace g3=1 if GOS6m=="3"



*generate obs
gen obs=_n

*transfer data from wide to long
reshape long g, i(obs) j(time)

*transfer time as 1, 3, 6 months (time2 as core covariate)
gen time2=.
replace time2=1 if time==1
replace time2=3 if time==2
replace time2=6 if time==3

*transfer Age, Treatment, WFNS, Fisher, Hp from string to numeric data
destring Age, gen(age)
destring Treatment, gen(treatment)
destring WFNS, gen(wfns)
destring Fisher, gen(fisher)
gen hpp=.
```

```
replace hpp=0 if Hp=="1"

replace hpp=0 if Hp=="2"

replace hpp=1 if Hp=="3"


**logistic regression on Study E_unadj

logistic g i.hpp if Study_ID=="E"


**logistic regression on Study E_adj

logistic g i.hpp diabetes htn a1 age i.treatment1 i.fisher i.wfns if Study_ID=="E"


**sliding dichotomy for Study E

logistic g i.treatment1  htn age i.fisher i.wfns if Study_ID=="E"

predict phatE if Study_ID=="E" & time2==6

xtile phate=phatE, nquantiles(3)

gen dichotomy=.

replace dichotomy=1 if Study_ID=="E"&(g==1|g==0)&time2==6

replace dichotomy=0 if GOS6m=="5"& Study_ID=="E" & time2==6

replace dichotomy=0 if GOS6m=="4"&Study_ID=="E" & time2==6 &(phate==2|phate==3)

replace dichotomy=0 if GOS6m=="3"&Study_ID=="E" & time2==6 &(phate==3)

**study E overall

logistic dichotomy i.hpp i.treatment1 age i.fisher i.wfns if Study_ID=="E"


**ordinal outcome
```

```
gen og=.
replace og=2 if GOS30d=="4" & time2==1
replace og=1 if GOS30d=="5" & time2==1
replace og=3 if GOS30d=="3" & time2==1
replace og=3 if GOS30d=="2" & time2==1
replace og=3 if GOS30d=="1" & time2==1

replace og=2 if GOS3m=="4" & time2==3
replace og=1 if GOS3m=="5" & time2==3
replace og=3 if GOS3m=="3" & time2==3
replace og=3 if GOS3m=="2" & time2==3
replace og=3 if GOS3m=="1" & time2==3

replace og=2 if GOS6m=="4" & time2==6
replace og=1 if GOS6m=="5" & time2==6
replace og=3 if GOS6m=="3" & time2==6
replace og=3 if GOS6m=="2" & time2==6
replace og=3 if GOS6m=="1" & time2==6

ologit og i.hpp i.treatment1 age i.fisher i.wfns diabetes a1 htn if Study_ID=="E", cluster(obs) or
```

APPENDIX C: RELEVANT STATA CODES (secondary outcome)

```
import excel "D:\pitt\study\Project-Meta\part 2\IPLD_coded_combined_ANALYSIS_pitt_080117 (1).xlsx", sheet("Data") firstrow clear

drop if Treatment == 3
gen hpp=.
replace hpp=0 if Hp==1
replace hpp=0 if Hp==2
replace hpp=1 if Hp==3

* cross-sectional analysis of secondary outcome without adjusted-DIND
logit DIND i.hpp if Study_ID=="A", or
logit DIND i.hpp if Study_ID=="B", or
logit DIND i.hpp if Study_ID=="C", or
logit DIND i.hpp if Study_ID=="D", or
logit DIND i.hpp if Study_ID=="F", or
logit DIND i.hpp if Study_ID=="G", or
logit DIND i.hpp if Study_ID=="I", or
logit DIND i.hpp if Study_ID=="K", or
```

```
* cross-sectional analysis of secondary outcome without adjusted-Ran_inf
gen rad=.
replace rad=0 if Rad_inf=="0"
replace rad=1 if Rad_inf=="1"
logit rad i.hpp if Study_ID=="A", or
logit rad i.hpp if Study_ID=="B", or
logit rad i.hpp if Study_ID=="C", or
logit rad i.hpp if Study_ID=="D", or
logit rad i.hpp if Study_ID=="G", or

* cross-sectional analysis of secondary outcome without Def_VS
logit Def_VS i.hpp if Study_ID=="A", or
logit Def_VS i.hpp if Study_ID=="D", or
logit Def_VS i.hpp if Study_ID=="E", or
logit Def_VS i.hpp if Study_ID=="F", or
logit Def_VS i.hpp if Study_ID=="G", or
logit Def_VS i.hpp if Study_ID=="H", or
logit Def_VS i.hpp if Study_ID=="I", or

* cross-sectional analysis of secondary outcome without adjuasted--Angio_VS
logit Angio_VS i.hpp if Study_ID=="B", or
logit Angio_VS i.hpp if Study_ID=="C", or
logit Angio_VS i.hpp if Study_ID=="D", or
```

```
logit Angio_VS i.hpp if Study_ID=="F", or
logit Angio_VS i.hpp if Study_ID=="G", or
logit Angio_VS i.hpp if Study_ID=="I", or
logit Angio_VS i.hpp if Study_ID=="J", or
logit Angio_VS i.hpp if Study_ID=="K", or

***adjusted secondary outcome
gen a1=.
replace a1=1 if Aneurysm ==1
replace a1=2 if Aneurysm ==2
replace a1=3 if Aneurysm ==3
replace a1=4 if Aneurysm ==4
** cross-sectional analysis of secondary outcome with adjusted-DIND
logit DIND i.hpp Age i.WFNS i.Treatment i.HTN if Study_ID=="A", or
logit DIND i.hpp Age i.WFNS i.Treatment i.HTN if Study_ID=="B", or
logit DIND i.hpp Age i.WFNS i.Treatment i.HTN if Study_ID=="C", or
logit DIND i.hpp Age i.Fisher i.WFNS i.Treatment i.HTN if Study_ID=="D", or
logit DIND i.hpp Age if Study_ID=="F", or
logit DIND i.hpp Age i.WFNS i.Treatment i.HTN if Study_ID=="G", or
logit DIND i.hpp Age i.Fisher i.WFNS i.Treatment i.HTN if Study_ID=="I", or
logit DIND i.hpp Age i.Fisher i.Treatment i.HTN if Study_ID=="K", or
* cross-sectional analysis of secondary outcome with adjusted-Ran_inf
logit rad i.hpp i.a1 Age i.WFNS i.Treatment i.HTN if Study_ID=="A", or
```

```
logit rad i.hpp i.a1 Age i.WFNS i.Treatment i.HTN if Study_ID=="B", or
logit rad i.hpp i.a1 Age i.WFNS i.Treatment i.HTN if Study_ID=="C", or
logit rad i.hpp i.a1 Age i.WFNS i.Treatment i.HTN i.Fisher if Study_ID=="D", or
logit rad i.hpp i.a1 Age i.WFNS i.Treatment i.HTN i.Fisher if Study_ID=="G", or
* cross-sectional analysis of secondary outcome with adjusted_Def_VS
logit Def_VS i.hpp Age i.HTN if Study_ID=="A", or
logit Def_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="D", or
logit Def_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="E", or
logit Def_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="F", or
logit Def_VS i.hpp Age i.HTN i.WFNS if Study_ID=="G", or
logit Def_VS i.hpp Age if Study_ID=="H", or
logit Def_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="I", or
* cross-sectional analysis of secondary outcome with adjuasted--Angio_VS
logit Angio_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="B", or
logit Angio_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="C", or
logit Angio_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="D", or
logit Angio_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="F", or
logit Angio_VS i.hpp Age i.WFNS i.Fisher i.Treatment i.HTN if Study_ID=="I", or
logit Angio_VS i.hpp Age i.Treatment i.HTN if Study_ID=="J", or
logit Angio_VS i.hpp Age i.Treatment i.HTN if Study_ID=="K", or
```

APPENDIX D: RELEVANT STATA CODES (Meta-analysis)

```
** 22 vs 11&12 unadjusted
clear

set obs 8
gen or=0
gen lci=0
gen uci=0
gen name=""

replace or=0.478 in 1/1
replace or=1.267 in 2/2
replace or=0.799 in 3/3
replace or=1.195 in 4/4
replace or=0.909 in 5/5
replace or=0.725 in 6/6
replace or=2.244 in 7/7
replace or=1.549 in 8/8
```

```
replace lci=0.116 in 1/1
replace lci=0.577 in 2/2
replace lci=0.340 in 3/3
replace lci=0.242 in 4/4
replace lci=0.413 in 5/5
replace lci=0.354 in 6/6
replace lci=0.421 in 7/7
replace lci=0.817 in 8/8

replace uci=1.963 in 1/1
replace uci=2.785 in 2/2
replace uci=1.878 in 3/3
replace uci=5.914 in 4/4
replace uci=2.000 in 5/5
replace uci=1.486 in 6/6
replace uci=11.959 in 7/7
replace uci=2.936 in 8/8

replace name="Study A" in 1/1
replace name="Study B" in 2/2
replace name="Study C" in 3/3
replace name="Study D" in 4/4
replace name="Study E" in 5/5
```

```
replace name="Study F" in 6/6

replace name="Study G" in 7/7

replace name="Study I" in 8/8


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se,egger


***22 vs 11&12 same covariates

clear


set obs 8

gen or=0

gen lci=o

gen uci=0

gen name=""


replace or=0.467 in 1/1
```

replace or=1.001 in 2/2

replace or=0.695 in 3/3

replace or=1.017 in 4/4

replace or=1.106 in 5/5

replace or=0.672 in 6/6

replace or=1.770 in 7/7

replace or=0.994 in 8/8

replace lci=0.085 in 1/1

replace lci=0.116 in 2/2

replace lci=0.281 in 3/3

replace lci=0.100 in 4/4

replace lci=0.450 in 5/5

replace lci=0.262 in 6/6

replace lci=0.338 in 7/7

replace lci=0.454 in 8/8

replace uci=2.571 in 1/1

replace uci=8.628 in 2/2

replace uci=1.723 in 3/3

replace uci=10.363 in 4/4

replace uci=2.722 in 5/5

replace uci=1.725 in 6/6

```
replace uci=9.279 in 7/7

replace uci=2.177 in 8/8


replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study D" in 4/4

replace name="Study E" in 5/5

replace name="Study F" in 6/6

replace name="Study G" in 7/7

replace name="Study I" in 8/8


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger


gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


***sliding dichotomy_same covariates 22 vs 11&12
```

```
clear

set obs 6

gen or=0

gen lci=0

gen uci=0

gen name=""

replace or=0.198 in 1/1

replace or=2.633 in 2/2

replace or=0.748 in 3/3

replace or=1.219 in 4/4

replace or=1.036 in 5/5

replace or=0.957 in 6/6

replace lci=0.039 in 1/1

replace lci=0.960 in 2/2

replace lci=0.294 in 3/3

replace lci=0.568 in 4/4

replace lci=0.380 in 5/5

replace lci=0.409 in 6/6

replace uci=1.005 in 1/1
```

```
replace uci=7.223 in 2/2

replace uci=1.907 in 3/3

replace uci=2.619 in 4/4

replace uci=2.824 in 5/5

replace uci=2.241 in 6/6


replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study E" in 4/4

replace name="Study F" in 5/5

replace name="Study I" in 6/6


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


***ordinal_22vs11&12_same
```

```
clear

set obs 8

gen or=0

gen lci=0

gen uci=0

gen name=""

replace or=0.315 in 1/1

replace or=0.988 in 2/2

replace or=0.799 in 3/3

replace or=2.298 in 4/4

replace or=1.356 in 5/5

replace or=0.694 in 6/6

replace or=0.746 in 7/7

replace or=0.823 in 8/8

replace lci=0.073 in 1/1

replace lci=0.448 in 2/2

replace lci=0.353 in 3/3

replace lci=0.527 in 4/4

replace lci=0.721 in 5/5

replace lci=0.353 in 6/6
```

```
replace lci=0.203 in 7/7

replace lci=0.464 in 8/8


replace uci=1.354 in 1/1

replace uci=2.181 in 2/2

replace uci=1.810 in 3/3

replace uci=10.020 in 4/4

replace uci=2.550 in 5/5

replace uci=1.365 in 6/6

replace uci=2.744 in 7/7

replace uci=1.462 in 8/8


replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study D" in 4/4

replace name="Study E" in 5/5

replace name="Study F" in 6/6

replace name="Study G" in 7/7

replace name="Study I" in 8/8


gen lnor=ln(or)

gen lnlci=ln(lci)
```

```
gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


**DIND 22 VS 11&12 unadjusted

clear


set obs 6

gen or=0

gen lci=0

gen uci=0

gen name=""


replace or=0.545 in 1/1

replace or=2.458 in 2/2

replace or=1.367 in 3/3

replace or=0.844 in 4/4

replace or=1.45 in 5/5

replace or=1.335 in 6/6
```

```
replace lci=0.093 in 1/1

replace lci=0.897 in 2/2

replace lci=0.522 in 3/3

replace lci=0.219 in 4/4

replace lci=0.236 in 5/5

replace lci=0.716 in 6/6


replace uci=3.194 in 1/1

replace uci=6.736 in 2/2

replace uci=3.578 in 3/3

replace uci=3.255 in 4/4

replace uci=8.923 in 5/5

replace uci=2.488 in 6/6


replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study D" in 4/4

replace name="Study G" in 5/5

replace name="Study I" in 6/6


gen lnor=ln(or)

gen lnlci=ln(lci)
```

```
gen lnuci=ln(uci)
metan lnor lnlci lnuci, eform effect(or) label(namevar=name)

metafunnel or lci uci, eform egger
gen se=(lnuci-lnor)/1.96
metabias lnor se, egger

***DIND 22vs11&21_same
clear

set obs 8
gen or=0
gen lci=0
gen uci=0
gen name=""

replace or=0.455 in 1/1
replace or=2.201 in 2/2
replace or=1.556 in 3/3
replace or=0.690 in 4/4
replace or=1.566 in 5/5
replace or=1.788 in 6/6
replace or=0.907 in 7/7
```

replace or=0.393 in 8/8

replace lci=0.070 in 1/1

replace lci=0.772 in 2/2

replace lci=0.551 in 3/3

replace lci=0.146 in 4/4

replace lci=0.062 in 5/5

replace lci=0.248 in 6/6

replace lci=0.430 in 7/7

replace lci=0.027 in 8/8

replace uci=2.947 in 1/1

replace uci=6.274 in 2/2

replace uci=4.395 in 3/3

replace uci=3.263 in 4/4

replace uci=39.515 in 5/5

replace uci=12.884 in 6/6

replace uci=1.912 in 7/7

replace uci=5.584 in 8/8

replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

```
replace name="Study D" in 4/4

replace name="Study F" in 5/5

replace name="Study G" in 6/6

replace name="Study I" in 7/7

replace name="Study K" in 8/8


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


**Rad_inf 11&12vs22-unadjusted

clear


set obs 5

gen or=0

gen lci=0

gen uci=0

gen name=""
```

replace or=0.900 in 1/1

replace or=2.103 in 2/2

replace or=0.652 in 3/3

replace or=1.25 in 4/4

replace or=1.26 in 5/5

replace lci=0.184 in 1/1

replace lci=0.659 in 2/2

replace lci=0.161 in 3/3

replace lci=0.316 in 4/4

replace lci=0.248 in 5/5

replace uci=4.400 in 1/1

replace uci=6.704 in 2/2

replace uci=2.644 in 3/3

replace uci=4.940 in 4/4

replace uci=6.446 in 5/5

replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study D" in 4/4

```
replace name="Study G" in 5/5

gen lnor=ln(or)
gen lnlci=ln(lci)
gen lnuci=ln(uci)
metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random

metafunnel or lci uci, eform egger
gen se=(lnuci-lnor)/1.96
metabias lnor se, egger

***Rad_inf_22 vs 11 & 12_same covariates
clear

set obs 5
gen or=0
gen lci=0
gen uci=0
gen name=""

replace or=1.027 in 1/1
replace or=1.934 in 2/2
replace or=0.832 in 3/3
```

```
replace or=1.390 in 4/4

replace or=0.905 in 5/5


replace lci=0.176 in 1/1

replace lci=0.573 in 2/2

replace lci=0.183 in 3/3

replace lci=0.296 in 4/4

replace lci=0.136 in 5/5


replace uci=6.013 in 1/1

replace uci=6.533 in 2/2

replace uci=3.773 in 3/3

replace uci=6.535 in 4/4

replace uci=5.999 in 5/5


replace name="Study A" in 1/1

replace name="Study B" in 2/2

replace name="Study C" in 3/3

replace name="Study D" in 4/4

replace name="Study G" in 5/5


gen lnor=ln(or)

gen lnlci=ln(lci)
```

```
gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


***Def_VS 22vs11&12 same covariates

clear


set obs 7

gen or=0

gen lci=0

gen uci=0

gen name=""


replace or=0.463 in 1/1

replace or=0.978 in 2/2

replace or=0.715 in 3/3

replace or=0.669 in 4/4

replace or=4.518 in 5/5

replace or=0.454 in 6/6

replace or=1.079 in 7/7
```

```
replace lci=0.041 in 1/1

replace lci=0.125 in 2/2

replace lci=0.256 in 3/3

replace lci=0.270 in 4/4

replace lci=0.237 in 5/5

replace lci=0.040 in 6/6

replace lci=0.525 in 7/7


replace uci=5.279 in 1/1

replace uci=7.619 in 2/2

replace uci=2.000 in 3/3

replace uci=1.657 in 4/4

replace uci=85.951 in 5/5

replace uci=5.139 in 6/6

replace uci=2.218 in 7/7


replace name="Study A" in 1/1

replace name="Study D" in 2/2

replace name="Study E" in 3/3

replace name="Study F" in 4/4

replace name="Study G" in 5/5

replace name="Study H" in 6/6
```

```
replace name="Study I" in 7/7

gen lnor=ln(or)
gen lnlci=ln(lci)
gen lnuci=ln(uci)
metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random

metafunnel or lci uci, eform egger
gen se=(lnuci-lnor)/1.96
metabias lnor se, egger

***Def_VS 22vs11&12 same covariates
clear

set obs 7
gen or=0
gen lci=0
gen uci=0
gen name=""

replace or=0.463 in 1/1
replace or=0.978 in 2/2
replace or=0.715 in 3/3
```

replace or=0.669 in 4/4

replace or=4.518 in 5/5

replace or=0.454 in 6/6

replace or=1.079 in 7/7

replace lci=0.041 in 1/1

replace lci=0.125 in 2/2

replace lci=0.256 in 3/3

replace lci=0.270 in 4/4

replace lci=0.237 in 5/5

replace lci=0.040 in 6/6

replace lci=0.525 in 7/7

replace uci=5.279 in 1/1

replace uci=7.619 in 2/2

replace uci=2.000 in 3/3

replace uci=1.657 in 4/4

replace uci=85.951 in 5/5

replace uci=5.139 in 6/6

replace uci=2.218 in 7/7

replace name="Study A" in 1/1

replace name="Study D" in 2/2

```
replace name="Study E" in 3/3

replace name="Study F" in 4/4

replace name="Study G" in 5/5

replace name="Study H" in 6/6

replace name="Study I" in 7/7


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger


**Angio_VS 11 & 12 vs 22-unadjusted

clear


set obs 7

gen or=0

gen lci=0

gen uci=0

gen name=""
```

replace or=3.597 in 1/1

replace or=1.623 in 2/2

replace or=0.844 in 3/3

replace or=1.097 in 4/4

replace or=0.620 in 5/5

replace or=2 in 6/6

replace or=1.333 in 7/7

replace lci=1.492 in 1/1

replace lci=0.514 in 2/2

replace lci=0.219 in 3/3

replace lci=0.456 in 4/4

replace lci=0.277 in 5/5

replace lci=0.324 in 6/6

replace lci=0.165 in 7/7

replace uci=8.668 in 1/1

replace uci=5.125 in 2/2

replace uci=3.255 in 3/3

replace uci=2.638 in 4/4

replace uci=1.387 in 5/5

replace uci=12.329 in 6/6

```
replace uci=10.743 in 7/7

replace name="Study B" in 1/1
replace name="Study C" in 2/2
replace name="Study D" in 3/3
replace name="Study F" in 4/4
replace name="Study I" in 5/5
replace name="Study J" in 6/6
replace name="Study K" in 7/7

gen lnor=ln(or)
gen lnlci=ln(lci)
gen lnuci=ln(uci)
metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random

metafunnel or lci uci, eform egger
gen se=(lnuci-lnor)/1.96
metabias lnor se, egger

***Angio_vs 22vs11&12 same covariates
clear

set obs 7
```

```
gen or=0

gen lci=0

gen uci=0

gen name=""


replace or=3.268 in 1/1

replace or=2.203 in 2/2

replace or=0.690 in 3/3

replace or=0.776 in 4/4

replace or=0.452 in 5/5

replace or=1.834 in 6/6

replace or=0.453 in 7/7


replace lci=1.293 in 1/1

replace lci=0.612 in 2/2

replace lci=0.146 in 3/3

replace lci=0.265 in 4/4

replace lci=0.182 in 5/5

replace lci=0.221 in 6/6

replace lci=0.033 in 7/7


replace uci=8.262 in 1/1

replace uci=7.936 in 2/2
```

```
replace uci=3.263 in 3/3

replace uci=2.273 in 4/4

replace uci=1.122 in 5/5

replace uci=15.176 in 6/6

replace uci=6.294 in 7/7


replace name="Study B" in 1/1

replace name="Study C" in 2/2

replace name="Study D" in 3/3

replace name="Study F" in 4/4

replace name="Study I" in 5/5

replace name="Study J" in 6/6

replace name="Study K" in 7/7


gen lnor=ln(or)

gen lnlci=ln(lci)

gen lnuci=ln(uci)

metan lnor lnlci lnuci, eform effect(or) label(namevar=name) random


metafunnel or lci uci, eform egger

gen se=(lnuci-lnor)/1.96

metabias lnor se, egger
```

APPENDIX E: RELEVANT STATA CODES (one-stage analysis)

```
**primary outcome

gen primary=.

replace primary=m

replace primary=g if Study_ID=="E"

**unadjusted

melogit primary i.hpp ||obs:,||Study_ID:, or

**adjusted

melogit primary i.hpp age i.wfns i.treatment||obs:,||Study_ID:, or


**secondary outcome

***one-stage unadj

melogit DIND i.hpp ||Study_ID:, or

melogit rad i.hpp ||Study_ID:, or

melogit Angio_VS i.hpp||Study_ID:, or

melogit Def_VS i.hpp||Study_ID:, or

melogit second i.hpp||Study_ID:, or
```

***one-stage adj

melogit DIND i.hpp Age i.WFNS i.Treatment i.HTN ||Study_ID:,or

melogit rad i.hpp Age i.WFNS i.Treatment i.HTN ||Study_ID:,or

melogit Angio_VS i.hpp Age i.WFNS i.Treatment i.HTN ||Study_ID:,or

melogit Def_VS i.hpp Age i.WFNS i.Treatment i.HTN ||Study_ID:,or

melogit second i.hpp Age i.WFNS i.Treatment i.HTN ||Study_ID:,or

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