# COMPARISON OF RISK RATIO IN HEMORRHOIDS PATIENTS TREATED BY *CISSUS QUADRANGULARIS* L. VERSUS THE CONVENTIONAL TREATMENT

**JITTIMA LEELATHEERAKUL**

**A THESIS SUBMITTED IN PARTIAL FULFILLMENT**
**OF THE REQUIREMENTS FOR**
**THE DEGREE OF MASTER OF SCIENCE (BIOSTATISTICS)**
**FACULTY OF GRADUATE STUDIES**
**MAHIDOL UNIVERSITY**
**2005**

**ISBN 974-04-6221-9**
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was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Master of Science (Biostatistics)
on
May 18, 2005

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# ACKNOWLEDGEMENT

I would like to express my sincere gratitude and deep appreciation to my major advisor, Associate Professor Dr. Dechavudh Nityasuddhi, for his guidance, invaluable advice, supervision and encouragement throughout the thesis. He was never lacking in kindness and support. I am equally grateful to Assistant Professor Dr. Junya Pattaraarchachai my co-advisor for her invaluable suggestion, constant support and warm encouragement. They have sacrificed their time to give advice and had the grace to correct mistakes and make improvements so that this study came out wholly complete.

I am very special thanks to Associate Professor Dr. Pannawish Wongwiwattananon for his kindness and helpful comments. And special unforgettable thanks also to everybody in the Department of Biostatistics, Faculty of Public Health.

Finally, I am extremely grateful to my family for their love, kindness, understanding and cheering throughout this study. My sincere thanks are given to my lovely friends for their assistance and kindly support.

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COMPARISON OF RISK RATIO IN HEMORRHOIDS PATIENTS TREATED BY *CISSUS QUADRANGULARIS L.* VERSUS THE CONVENTIONAL TREATMENT

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## ABSTRACT

The purpose of this study was to evaluate the effects of *Cissus quadrangularis L.* (Pet-sang-kart) versus the conventional treatment for curing hemorrhoids patients. Secondary data from a phase III clinical trial were used in a logistic regression model. The data consisted of 526 patients with hemorrhoids, of whom 52 experienced an improvement in the severity of hemorrhoids, while 474 did not.

The selected model could explain 12.5% of total variation and an adjusted risk ratio was estimated. The model included severity of hemorrhoids, treatment (Pet-sang-kart, Daflon, and placebo) and interaction of hemorrhoid severity with treatments. The risk ratio result showed that patients with severe hemorrhoids who used Pet-sang-kart had 1.46 times greater improvement in severe hemorrhoid symptoms, compared with patients who received the other treatments (risk ratio = 1.46), while other risk ratio values were close to 1 (risk ratio = 1.07, 0.95 for Pet-sang-kart and Daflon, in moderate hemorrhoid patients, respectively).

KEY WORDS : ADJUSTED RISK RATIO / LOGISTIC REGRESSION /
HEMORRHOIDS / *CISSUS QUADRANGULARIS L.*

69 P. ISBN 974-04-6221-9

การเปรียบเทียบอัตราส่วนความเสี่ยง (RISK RATIO) ของผู้ป่วยโรคริดสีดวงทวารที่รักษาด้วยการใช้สมุนไพรเพชรสังฆาตกับการรักษาแบบปกติ (COMPARISON OF RISK RATIO IN HEMORRHOIDS PATIENTS TREATED BY *CISSUS QUADRANGULARIS L.* VERSUS THE CONVENTIONAL TREATMENT)

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**บทคัดย่อ**

การศึกษาครั้งนี้ มีวัตถุประสงค์ เพื่อประเมินผลการรักษาของสมุนไพรเพชรสังฆาตเปรียบเทียบกับยารักษาโรคริดสีดวงทวารในผู้ป่วยโรคริดสีดวงทวาร ซึ่งใช้ข้อมูลทุติยภูมิจากการศึกษาวิจัยทางคลินิกระยะที่ 3 โดยใช้ตัวแบบการถดถอยพหุโลจิสติก ซึ่งศึกษาในผู้ป่วยที่มีอาการริดสีดวงทวารจำนวน 526 ราย จำแนกเป็นผู้ป่วยที่มีอาการดีขึ้นหลังจากทำการรักษามีจำนวน 52 ราย และผู้ป่วยที่อาการไม่ดีขึ้นหลังจากทำการรักษามีจำนวน 474 ราย

จากตัวแบบการถดถอยพหุโลจิสติกที่เลือกได้สามารถอธิบายการเปลี่ยนแปลงของอัตราส่วนความเสี่ยงได้ร้อยละ 12.5 ซึ่งตัวแบบประกอบด้วยความรุนแรงของโรคริดสีดวงทวารก่อนการรักษา วิธีการรักษา (สมุนไพรเพชรสังฆาต ยาแดฟลอน และ ยาหลอก) และ ปฏิสัมพันธ์ระหว่างความรุนแรงของโรคก่อนการรักษา กับ วิธีการรักษา ผลการศึกษาของอัตราส่วนความเสี่ยงสามารถแสดงได้ว่า ผู้ป่วยริดสีดวงทวารที่มีอาการรุนแรง เมื่อได้รับสมุนไพรเพชรสังฆาตในการรักษาโรค ผู้ป่วย จะมีอาการริดสีดวงทวารดีขึ้นเป็น 1.46 เท่า เมื่อเปรียบเทียบผู้ป่วยที่ได้รับยาอื่นในการรักษา (อัตราส่วนความเสี่ยงเป็น 1.46 เท่า) ขณะที่ค่าอัตราส่วนความเสี่ยงของสมุนไพรเพชรสังฆาต และ ยาแดฟลอนในการรักษาผู้ป่วยริดสีดวงทวารที่มีอาการไม่รุนแรงมากนักมีค่าเข้าใกล้หนึ่ง (อัตราส่วนความเสี่ยงเป็น 1.07 และ 0.95เท่า) ตามลำดับ

69 หน้า. ISBN 974-04-6221-9

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# CHAPTER I
# INTRODUCTION

## 1.1 Rationale and justification

In an era of well-developed technologies, a variety of treatments have been invented to cure diseases. Among these treatments, natural herbs have also been of interest. In general, a basic factor in treatment is the use of herbs that contain an important drug (1,2). Herbs are considered local natural resources, and Thais have long and commonly used herbs in medical treatments. Even today, herbs are still used in both urban and rural areas, especially remote ones (3).

During the past century, the use of herbal medicine in Thailand has been on the decline, due largely to the introduction of modern medicine which is more effective and easier to use. However, there is a worldwide trend toward the use of drugs of natural origin since they are believed to possess less harmful side effects than synthetic drugs. This has resulted in an increased public awareness of the rich and valuable heritage of traditional Thai medicine. There has also been a concerted effort by government and private sectors to develop Thai medicinal plants into safe and effective drugs. Examples of these endeavours are the development of an anti-asthmatic drug from "plai" (*Zingiber cassumunar* Roxb.*)*, an antipeptic-ulcer drug from "plaunoi" *(Croton sublyratus* Kurz*)* and a drug from goat's foot creeper (*Ipomoea pes-caprae*(Linn.) Sweet*)* for jellyfish poison (4).

Thai people are justly proud of the wealth of knowledge in traditional Thai medicine and their rich natural resources. Every attempt will be made to effect the appropriate development of Thai medicinal plants for the benefit of mankind (3). *Cissus quadrangularis* Linn. *(C. quadrangularis)*, commonly known in Thailand as "Phet-Cha-Sung-Khaat", is a climber that belongs to the Vitaceae family, and is one among the most frequently used medicinal plants in Thailand, which can be found throughout the country (5). The stout fleshy quadrangular stem of *C.quadrangularis* is

traditionally used for treating hemorrhoids and irregular menstruation, and also to accelerate healing of bone fracture (6).

Hemorrhoids is a condition that has been known and treated for at least 4000 years but has only recently come to be partially understood. The word “hemorrhoids” is derived from the Greek adjective haimorrhoides, which means bleeding (haima = blood; rhoos = flowing). The word pile is derived from the Latin word pila, meaning a ball. The two words, hemorrhoids and piles, have become misused over time, and have come to be used by laypeople for many of the conditions and symptoms associated with the perianal region (7).

A nationwide questionnaire indecated ten million people in the United States complaining of hemorrhoids, corresponding to a prevalence rate is 4.4% (8). A similar questionnaire in a London general practice showed a prevalence of 36.4% (9). In the United States, physicians have reported 1177 visits for hemorrhoids per 100,000 population per year. Data from England and Wales showed similar figures, with 1123 visits per 100,000 population, per year. There appears to be a peak incidence in middle age with a decline after the age of 65 (9). The annual rate of office visits for hemorrhoids is 12/1,000 patients in the United States; its prevalence is similar between the sexs and increases with age until the seventh decade. Only a third of patients with symptomatic hemorrhoids seek medical help (9). The incidence rate of hemorrhoids is 5 % in Thailand. There appears to be a peak at 45-65 years of age and a little in less than 20 years (10).

Primary care physicians can safely use simple treatment measures to manage most cases of symptomatic hemorrhoids. Only the more symptomatic patients require surgical intervention (7). Treatments for hemorrhoids consist of conservative treatment, medical therapy non-operative treatment or outpatients treatment, and surgical treatment (7,9,11,12).

Conventional treatment is composed of dietary and lifestyle modification, increasing the intake of fiber is useful for softening motions, relieving constipation, and thus reducing straining. Lifestyle advice on avoiding straining and reading on the toilet should be emphasized (12). Medical treatment includes ointments, dietary supplementation with micronised semisynthetic flavonoids and drug (Daflon) (12).

Mild cases of hemorrhoids can be relieved by increasing dietary fiber and fluid intake, bathing the anus, or applying soothing creams or ointment (13).

Lifestyle changes are recommended to minimize prolonged straining during bowel movements, which is thought to contribute to the development of hemorrhoids. Preventing constipation also helps alleviate more severe hemorrhoids and can help to prevent future episodes. Although the role of certain foods in the pathogenesis of hemorrhoids or their acute exacerbation is accepted empirically, this has not been proved. Also, no firm evidence to date shows that increasing physical exercise, and personal hygiene are beneficial (9).

At present, in Thailand, a lot of research is being conducted into herbs, but most use experimental design and univariate analysis. Univariate analysis considers only one independent variable associated with a dependent variable, so this analysis does not account for other independent variables, whereas the multivariate analysis considers co-operate independent variables at the same time. The multivariate method can explain the factors associated with hemorrhoids patients treated by herbal medicine and modern medicine. So, the researcher is interested in multivariate method by logistic regression analysis.

## 1.2 Objectives

### General objectives

To assess the effect of *Cissus quadrangularis L.* (Pet-sang-kart) versus the conventional treatment after taking into account of other covariates, in curing hemorrhoids patients.

### Specific objectives

1. To select the best model which can explain the relationship between treatment and the chance of disease improvement.
2. To estimate the risk ratio parameters.

## 1.4 Operational definitions

**Bleeding** is described as bright red spotting on toilet tissue or as dripping in the toilet bowl and normally occurs at the end of defecation and separately from the stool (11).

**Constipation** is defined as an abnormally infrequent and / or difficult defecation (14).

**Defecation** is defined as the evacuation of faeces (14).

**Diarrhoea** is defined as an abnormal increase in the frequency and / or the liquidity of the stools (14).

**Family history** is refered to familial disease genetically transmitted disease in which the abnormal gene is recessive in character, so that neither parent is affected (being heterozygous and carrying only one abnormal gene) but those their children who inherit develop the condition (14).

**Icth** is defined as the cutaneous sensation that provokes the urge (14).

**Haemorrhoids or hemorrhoids** is defined as dilatation and varicosity of veins of the superior or rectal and inferior or anal heamorrhoidal plexuses. The pathological changes in the vessels are similar to those which occur in varicose veins elsewhere. Haemorrhoids, or plies, give rise to various symptoms, chiefly discomfort, pain, and bleeding. Internal piles (i.e. if the superior plexus) may prolapse, and external piles (inferior plexus) may become thrombosed. They can be successfully treated in variety of ways (usually by injection or surgery) (14).

**Herbs** are vascular non-woody plants, that is leafy plants with no persistent parts above the ground; alternatively they are plants used in medicine or cookery. A herb in the second sense need not to be a herb in the first, but usually is herbal remedies (14).

**Herbs** have been defined in The Drug Act 1967 as medicine derived from plants and animal that can be used in curing diseases and nourishing health.

**Polyp** is defined as tissue bulging from the surface of an organ. Although these growths are not normal, they often are not cause for concern. However, people who have polyps in the colon may have an increased risk of colorectal cancer (14).

**Prolapse** is defined as a falling or slipping down of an organ; when otherwise unqualified, it usually means prolapse of the uterus, a not uncommon condition in

multiparous women in which the uterine cervix descends to or beyond the vaginal orifice and sometimes the whole uterus is extruded (14).

**Rectal prolapse** is defined as through the anus occurs sometimes in children (14).

**Pruritus** is defined as itching, which may be generalized or localized to a particular area (e.g. pruritus vulvae, pruritus ani, etc.) (14).

# CHAPTER II
# LITERATURE REVIEW

For this study, the researcher reviewed relevant concepts, theories, and research on the following topics:

2.1 Hemorrhoids
- 2.1.1 Pathogenesis
- 2.1.2 Classification of hemorrhoids
- 2.1.3 Treatment of hemorrhoids
- 2.1.4 Herbal treatment in hemorrhoids (*Cissus quadrangularis* L.)

2.2 Factors related to hemorrhoids

2.3 Logistic regression analysis

## 2.1 Hemorrhoids

Hemorrhoids is defined as dilatation and varicosity of veins of the superior or rectal and inferior or anal heamorrhoidal plexuses.

### 2.1.1 Pathogenesis

Hemorrhoids were normal anatomic features of the human anal canal, forming pads that bulge into the lumen. The anorectal area has a mucosal lining, a framework composed of blood vessels, smooth muscle and supporting tissues, as well as an anchoring connective tissue system that secures the hemorrhoidal tissues to the internal sphincters. This hemorrhoidal system is reported to cushion the anal canal during defecation (15).

Hemorrhoids were associated with chronic strainning secondary to constipation, diarrhea, tenesmus, or long periods trying to defecate, and are common during pregnancy and childbirth. The most common symptoms of hemorrhoids are bleeding and prolapse. Less frequently, symptoms also include discomfort, pain, soiling, or

itching (9). The blood is typically bright red and may frequently drip or squirt into the toilet bowl (11).

### 2.1.2 Classification of hemorrhoids

Hemorrhoids are classified by their point of origin: internal hemorrhoids and external hemorrhoids.

**Internal Hemorrhoids:** Internal hemorrhoids were usually painless; bleeding or prolapse generally prompt a visit to the physician (9). Hemorrhoids originating above the junction, even if prolapsed, are still classified as internal hemorrhiods, and are divided into 4 categories depending on the grade of porlapse:

Grade I Protrudes into the anal canal but does not prolapse.
Grade II Prolapses but reduces spontaneously.
Grade III Prolapses and requires manual reduction.
Grade IV Irreducible prolapse.

**External Hemorrhoids:** External hemorrhoids were swollen areas of skin and blood vessels around the anus (below the dentate line). They are lined with squamous epithelium that is highly innervated and sensitive. These particular hemorrhoids are also at risk for thrombosis. When internal and external hemorrhoids occur simultaneously, they are referred to as mixed hemorrhoids (16,17).

### 2.1.3 Treatment of hemorrhoids

Conventional treatment is composed of dietary and lifestyle modification, increasing the intake of fiber is useful for softening motions, relieving constipation, and thus reducing straining. Lifestyle advice on avoiding straining and reading on the toilet should be emphasized (12). Medical treatment includes ointments, dietary supplementation with micronised semisynthetic flavonoids and drug (Daflon) (12). Mild cases of hemorrhoids can be relieved by increasing dietary fiber and fluid intake, bathing the anus, or applying soothing creams or ointment (13).

Nonoperative treatment were injection sclerotherapy, cryotherapy, rubber band ligation, photocoagulation, elctrocoagulation and laser (7,11). Interventional

procedures are performed in clinic to treat first degree haemorrhoids that do not respond to dietary modification as well as second and third degree haemorrhoids (12). Surgical hemorrhoidectomy is the most effective treatment for hemorrhoids overall and for third-degree hemorrhoids in particular (11). A new surgical procedure, the stapled hemorrhoidectomy, has been shown to be effective, cause less pain, and require less time off from work compared with standard techniques (9).

Lifestyle changes are recommended to minimize prolonged straining during bowel movements, which is thought to contribute to the development of hemorrhoids. Preventing constipation also helps alleviate more severe hemorrhoids and can help to prevent future episodes. Although the role of certain foods in the pathogenesis of hemorrhoids or their acute exacerbation is accepted empirically, this has not been proved. Also, no firm evidence to date shows that increasing physical exercise, and personal hygiene are beneficial (9).

### 2.1.4 Herbal treatment in hemorrhoids (*Cissus quadrangularis* L.)

Thai people are justly proud of the wealth of knowledge in traditional Thai medicine and their rich natural resources. Every endeavour will be undertaken to effect appropriate development of Thai medicinal plants for the benefit of mankind (3). The use of medicinal plants was an alternative way for Thai people to take care of their own health because of their low cost, easy access and, most of all, their use since ancient times. The herb *Cissus quadrangularis* Linn. has been widely used as antihemorrhoid preparations in Thailand.

***Cissus quadrangularis* L.**

Scientific name : *Cissus quadrangularis* Linn.

Family : VITACEAE

Sample of local names : Pet-sang-kart (Central of Thailand), Khan-khoa (Rayong), Sam-roi-tor (Prajuab Kirikhan)

**Botanical description**

Cissus quadrangularis Linn. is a common perennial climber conspicuous by its fleshy quadrangular stems. It looks like cactus-like, jointed climber, with tendrils. The stems are leafless when old, quadrangular and ridged. The flowers are in short cymes and greenish-yellow, and the fruit is a globose berry (18,19).

**Medical property**

Roots : acceleration of fractured bones.

Stem : stem juice is beneficial as alterative in scurvy and irregular menstruation, and in diseases of the ear and in nose bleeding
A paste of the stem is given in asthma, and may be useful for muscular pains, burns and wounds, bites of poisonous insects and for saddle sores of horses and camels.

Shoots : young shoots are used in treatment of dyspepsia and indigestion and considered as to be powerful alterative.
The powder of dry shoots is given in digestive troubles, hemorrhoids.

**Phytoactive :**

From the plant stems,3-ketosteroids have been isolated. Two unsymmetric tetracyclic triterpenoids, sitosterol, a -amyrin and b-amyrene have also been isolated. The steroid contained in this plant has an anabolic property.It is used as a digestive. Crushed stems are used as a poultice over bone fractures. The powdered stem is mixed with pulses and fried in sesame oil, as a remedy for several vata diseases.

**Reviews of *Cissus quadrangularis* L.**

Tiangburanatham W. (20) has reported that 100 g of fresh stem contained about 267 mg of carotene, 398 mg of vitamin C and a lot of calcium oxalate crystals.

Segsunviriya C. and Choomprabutra S. (21) conducted a clinical trial of *Cissus qudrangularis L.* for the treatment of hemorrhoid and found that it was effective.

Yoganarsimhan S.N. (22) reported the plant has been documented in Ayurveda for its medicinal uses in gout, syphilis, venereal disease, piles, leucorrhoea and as an aphrodisiac, and in the Siddha system of medicine for the treatment of piles, diarrhoea and dysentery and in diseases of kapham.

## 2.2 Factors related to hemorrhoids

The factors which related hemorrhoids with each variable were reviewed for presentation in this paper.

### Age

Stewart et al.(23) examined the association with constipation in 3,166 persons over age 65 years. The result from analysis with stepwise logistic regression was found that constipation was significantly associated with increasing age (OR=1.25, 95% CI[1.15-1.37]).

Johanson and Sonnenberg (24) performed a case-control study of 168 patients with internal hemorrhoids and 157 controls, using univariate analysis. It was shown that the prevalence of hemorrhoids in over age 65 years was not significantly associated with hemorrhoids (OR= 0.8, 95% CI [0.5-1.2]).

Delco and Sonnenberg (25) evaluated the association between hemorrhoids and constipation or diseases that cause diarrhea. Data obtained from VA hospital from 1986 until 1996. A total of 96,314 patients with hemorrhoids and the same number of control were random sampling of 100 cases and 100 controls. The result from analysis with un-paired t-test was found that patients with hemorrhoids was slightly older compared with controls ($t = 7.78,99$, $P < 0.001$).

Zaheer et al.(26) studied the risk factors for urinary retention after operations for benign anorectal diseases with stepwise logistic regression. A total of 1,026 consecutive operations from 1989 to 1994 comprised GroupI 382 patients with hemorrhoidectomy and GroupII 645 patients with other procedures. It was found that over age 47 years with hemorrhoidectomy was a significant risk factor for urinary retention (OR= 3.1, 95% CI [1.40-6.67]).

Ho et al.(27) studied micronized purified flavonidic fraction in the management of bleeding nonprolapsed hemorrhoids. This study was prospective randomized controlled trial. A total of 162 patients from Singapore General Hospital contained group I 66 patients was taken fiber, group II 57 patients rubber band ligation with fiber and MPFF group 39 patients received MPFF (Dalfon 500 mg plus fiber). A Wilcoxon

signed-rank test was used for the study. It was found that age was no significant between three groups.

Arbman et al.(29) compared two groups, 38 patients closed (Ferguson) Hemorrhoidec-tomy, 39 patients open (Ferguson) hemorrhoidectomy. The result from analysis with t-test and chi-squared test was found that age was no difference between two groups.

Menanna and Platell (30) conducted a prospective study of all patients under the age of 55 years refferred to a community-based teaching hospital with chronic, bright red, rectal bleeding from November 1997 to June 2000. A simple logistic regression analysis was used for the study. It was shown that mean age 39 ± 9 years (mean ± SD, range: 22-25 years) and age was not significantly associated between the presence of adenomas.

Ho et al.(31) studied the assessment any benefits, compare with a conventional open diathermy technique. A total of 119 consecutive patients with prolapsed irreducible hemorrhoids contained 62 conventional open diathermy technique and 57 stapled hemorrhoidectomy. The result from analysis with Fisher's exact was showed that no difference between two groups in age.

**Gender**

Stewart et al.(23) examined the association with constipation in 3,166 persons over age 65 years using stepwise logistic regression. It was reported that women were significantly associated with constipation more often than men (OR= 0.61, 95% CI [0.49-0.77]).

Johanson and Sonnenberg (24) conducted a case-control study in the Milwaukee VA Medical Center during 1989, with 85 patients with internal hemorrhoids reported symtoms of rectal bleeding, 83 patients with internal hemorrhoids and 157 controls, using univariate analysis. This study found that sex was not significantly associated with hemorrhoids (OR= 0.4, 95% CI [0.3-0.7]).

Delco and Sonnenberg (25) studied the association between hemorrhoids and other diagnoses. Data obtained in 100 patients with the primary or secondary diagnosis of hemorrhoids and 100 controls using chi-squared test. It was shown that male was significantly associated with hemorrhoids (chi-square = 111.5, 99, $P < 0.001$).

Zaheer et al.(26) studied the risk factors for urinary retention after operations for benign anorectal diseases with stepwise logistic regression. A total of 1,026 consecutive operations from 1989 to 1994 comprised group I 382 patients with hemorrhoidectomy and group II 645 patients with other procedures. It was found that male was independent risk factor (OR =1.7, P =0.02).

Chen et al.(27) conducted a single institution prospective study of 4,880 consecutive closed hemorrhoidectomies between January 1994 and July 1996. The result from analysis with multiple logistic regression was that male was an association with develop posthemorrhoidectomy secondary hemorrhage (relative risk=2.1, 95% CI [1.1- 4.1]).

Ho et al.(28) compared three groups, 66 patients was taken fiber, 57 patients rubber band ligation with fiber and 39 patients received MPFF (Dalfon 500 mg plus fiber). A Wilcoxon signed-rank test was used for the study. It was found that gender was no significant between three groups.

Arbman et al.(29) compared two groups, 38 patients closed (Ferguson) Hemorrhoidec-tomy, 39 patients open (Ferguson) hemorrhoidectomy. Data were analyzed by t-test and chi-squared test.It was found that there was no difference between gender and two groups.

Menanna and Platell (30) studied the efficacy of performing a flexible sigmoidoscopy on patients with chronic, bright red, rectal bleeding who are at low risk for colorectal neoplasia and who on rigid sigmoidoscopy, were found to have an identifiable anal cause (e.g.hemorrhoids, fissure) for their bleeding. A total of 82 patients were entered into the trial, there were 52 men and 30 women (ratio 1.8:1). It was shown sex was not significantly associated between the presence of adenomas.

Ho et al.(31) studied the assessment any benefits, compare with a conventional open diathermy technique. A total of 119 consecutive patients with prolapsed irreducible hemorrhoids contained 62 conventional open diathermy technique and 57 stapled hemorrhoidectomy. The result from analysis with Wilcoxon test was showed that no difference between two groups in gender.

**Family history**

Johanson and Sonnenberg (24) examined the association with hemorrhoids in 168 patients with internal hemorrhoids and 157 controls using univariate analysis. The result was that family history was not significantly associated with hemorrhoids (OR= 0.4, 95% CI [0.3-0.7]).

Loder P.B. et al. (32) reviewed about race and religion, were reported a positive family history was common but may be biased if haemorrhoid sufferers have increased awareness of their parents' anal health. This is consistent with a greater inclination to report disease in the parent of the same sex. Even so, actual treatment for haemorrhoids is commoner in both parents of sufferers, which supports a genuine family association – albeit possibly because of dietary, cultural, behavioural and other environmental factors rather than genes.

**Race**

Johanson and Sonnenberg (24) performed a case-control study of 85 patients with hemorrhoids reported symptoms of rectal bleeding, 83 patients with hemorrhoids and 157 controls, using Woolf's method. It was found race was not significantly associated with hemorrhoids.

Delco and Sonnenberg (25) conducted a case-control study of 100 cases with the primary or secondary diagnosis of hemorrhoids and 100 controls. The result from analysis with chi-squared test was shown that white was significantly associated with hemorrhoids (chi-square = 20.16, 99, $P < 0.001$).

Loder P.B. et al. (32) reviewed about race and religion, were reported the low prevalence in Africa was discussed above. Whites in the USA self-report haemorrhoids 1-5 times more often than blacks but this was likely to be educational, cultural and socioeconomic, as black men had rates similar to those in the lowest socioeconomic group. Although a French study failed to show any racial association, non-French subjects were few and mostly southern European.

**Obesity**

Johanson and Sonnenberg (24) performed a case-control study of 168 patients with internal hemorrhoids and 157 controls, using multiple logistic regression. It was

revealed that obesity was significantly associated with hemorrhoids (OR= 1.6, 95% CI [0.9-2.6]).

**Socioeconomic status and occupation**

Loder P.B. et al. (32) reviewed about socioeconomic status and occupation as: people in higher socioeconomic groups more frequently report haemorrhoids, perhaps reflecting different knowledge and attitudes. Heavy labourers and people whose occupations require prolonged sitting or standing had been alleged to had haemorrhoids more often. Others had denied this association, but those affected may suffer more severely.

**Behavior and psychological factors**

Loder P.B. et al. (32) reviewed about behavior and psychological factors were detailed psychological studies were lacking. Why some patients suffer more and seek treatment while others remain phlegmatic was unknown. Diet, habits and body habits. Despite Burkitt's assertion. fibre intake and the prevalence of haemorrhoids were not associated. Nor had there been any increase in average fibre intake associated with the fall in the prevalence of haemorrhoids. Although other dietary factors had been implicated, data were not consistent. Smoking, alcohol consumption, coffee consumption, obesity and participation in certain sports were not associated with haemorrhoidal disease.

**Internal hemorrhoids**

Sumboonnanonda K. and Lertsithichai P.(33) conducted a prospective clinical study on hospital outpatients and studied the effect of Ginko biloba –Troxerutin – Heptaminol Hce for a week in adults (18-70 years old) with acute hemorrhoidal attacks in the ano-rectal clinic of the Department of Surgery, Ramathibodi Hospital Medical School during September 2000 and November 2001. 22 patients received 4 capsules of Ginko biloba – Troxerutin – Heptaminol Hce each day for 7 days. The majority of patients 77.26% had grade 1-2 internal hemorrhoids with a median acute symptom duration of 3 days.

Chaleoykitti B.(34) compared the cessation of bleeding and the complication between multiple and single ligation using high ligation technique. All first-visit patients with bleeding first-degree to third-degree internal hemorrhoids without any previous hemorrhoidal treatment between January 1997 and December 1998 were included in this prospective study.

**Constipation**

Stewart et al.(23) studied the association of constipation with hemorrhoids in 3,166 persons over age 65 years on July 1979 to June 1988, using stepwise logistic regression. It was reported that hemorrhoids was significantly associated with constipation (OR= 2.00, 95% CI[1.58-2.52]).

Johanson and Sonnenberg (24) studied the association of hemorrhoids with constipation 168 patients with internal hemorrhoids and 157 controls. The result from analysis with univariate analysis was that constipation was not an important etiological risk factor. So there was not association between constipation and hemorrhoids.

Delco and Sonnenberg (25) evaluated the association between constipation with hemorrhoids in 100 patients with hemorrhoids and 100 controls, using multiple logistic regression. It was found that constipation and related diseases were significantly associated with hemorrhoids (OR= 1.48, 95% CI [1.43-1.54]).

Chaiarelli P. et al (35) This study was to explore associations between constipation and factors such as hemorrhoids, parity, hormone and drug use etc. in the three large cohorts of Australian women using descriptive statistics and logistic regression. The prevalence of constipation was 14.1% (CI 13.5-14.7) in young women, 26.6% (CI 25.9-27.4) in middle-aged women, and 27%(CI 26.9-28.5) in the older women. The prevalence of hemorrhoids was 3.2% (CI 2.9-3.4 young), 17.7% (CI 17.1-18.4 middle-aged) and 18.3% (CI 17.6-19.0 older)

**Diarrhea**

Johanson and Sonnenberg (24) conducted a case-control study in the Milwaukee VA Medical Center during 1989, with 168 patients with internal hemorrhoids and 157

controls. The analysis by multiple logistic regression found that diarrhea was significantly associated with developing hemorrhoids (OR=2.1, 95% CI [1.2-3.9]).

Delco and Sonnenberg (25) evaluated the association between constipation with hemorrhoids in 100 patients with hemorrhoids and 100 controls, using multiple logistic regression. It was shown that diarrhea was significantly associated with hemorrhoids (OR =1.30, 95% CI [1.27-1.33]).

**Bleed**

Menanna and Platell (30) conducted a prospective study of all patients under the age of 55 years presenting with chronic, bright red, rectal bleeding from November 1997 to June 2000. A total of 82 patients were entered into the trial with performing a flexible sigmoidoscopy. The result from analysis with simple logistic regression was found that the anal cause of bleeding was haemorrhoid in 96%.

Ho et al (31) studied the assessment any benefits, compare with a conventional open diathermy technique. A total of 119 consecutive patients with prolapsed irreducible hemorrhoids contained 62 conventional open diathermy technique and 57 stapled hemorrhoidectomy. Conventional wounds remained unhealed with more bleeding ( CNV 3.3 (53.2%) vs STP 19(33.3%) ; $P < 0.05$) , using Fisher exact.

Mentes et al (36) investigated the efficacy of calcium dobesilate in treating acute of internal hemorrhoids using Fisher's exact and chi-squared test. This study was randomized double blind controlled. A total of 45 patients contained 29 patients treated with calcium dobesilate for two weeks and 16 patients in control with diet group. It was reported that a success rate of 86.21% with cessation of bleeding plus lack of severe antitis anoscopically at two weeks were achieved with calcium dobesilate compare with the 43.75% success rate of the control group (P=0.0051).

Misra et al (37) examined MPFF was effective in rapidly stopping the bleeding of internal haemorrhoids and preventing a relapse in double blind, randomized, placebo controlled study. In 100 outpatients with acute rectal bleeding of less than 3 days contained 50 patients received MPFF and 50 controls, using t-test. The study found

that MPFF had rapid cessation of bleeding and a reduced risk of relapse ($P< 0.01$, $P<0.05$).

Sumboonnanonda K. and Lertsithichai P.(33) studied to the assessment the clinical efficacy, compliance and safety of Ginko biloba –Troxerutin – Heptaminol Hce in the treatment of patients with acute hemorrhoidal attacks in Thailand. 22 patients received 4 capsules of Ginko biloba –Troxerutin – Heptaminol Hce each day for 7 days. The result from analysis with asymptomatic marginal homogeneity test was found that rectal bleeding was significantly reduced by the $7^{th}$ day ($P< 0.05$).

Chaleoykitti B.(34) compared the cessation of bleeding and the complication between multiple and single ligation using high ligation technique. All first-visit patients with bleeding first-degree to third-degree internal hemorrhoids without any previous hemorrhoidal treatment between January 1997 and December 1998 were included in this prospective study. A total 109 patients with bleeding internal hemorrhoids were randomly divided into 61 patients had multiple and 48 patients had single ligation groups, using chi-square tests. The cessation of bleeding in one week occurred in 96.7% of patients in the multiple group and 79% of patients in the single group ($P=0.004$).

**Pain**

Ho et al (31) studied the assessment any benefits, compared with a conventional open diathermy technique by Fisher's exact probability test. A total of 119 consecutive patients with prolapsed irreducible hemorrhoids contained 62 conventional open diathermy technique and 57 stapled hemorrhoidectomy. Conventional patients felt more pain during defecation ( CNV 5.1 (0.4) vs STP 2.6(0.4) ; $P < 0.05$) at two weeks.

Sumboonnanonda K. and Lertsithichai P.(33) conducted a prospective clinical study on hospital outpatients and studied the effect of Ginko biloba –Troxerutin – Heptaminol Hce for a week in adults (18-70 years old) with acute hemorrhoidal attacks in the ano-rectal clinic of the Department of Surgery, Ramathibodi Hospital Medical School during September 2000 and November 2001. 22 patients received 4 capsules of Ginko biloba –Troxerutin – Heptaminol Hce each day for 7 days. The

result from analysis with Wilcoxon signed-rank test was shown that pain was significantly reduced by the $7^{th}$ day ($P< 0.05$).

Chaleoykitti B.(34) compared the cessation of bleeding and the complication between multiple and single ligation using high ligation technique. All first-visit patients with bleeding first-degree to third-degree internal hemorrhoids without any previous hemorrhoidal treatment between January 1997 and December 1998 in Phramongkutklao hospital were included in this prospective study. A total 109 patients with bleeding internal hemorrhoids were randomly divided into 61 patients had multiple and 48 patients had single ligation groups, using chi-square tests. There was no difference between the multiple group and single group concerning postligation pain and tenesmus (6.5% *vs* 2%, P=0.532).

Gupta PJ.(38) compared an additional method in treating acutely imflammed piles. Ten tablets of trypsin and chymotrypsin (Chymoral forte, Elder Pharmaceuticals India) were powdered and were mixed with 30 g. of heparin (Thrombophobe, German Remedies Ltd, Germany) ointment. 67 patients received ointment treatment with an average hospital stay of 2 days, 22 patients were treated with the conventional method only, using chi-squared test. It was found that local pain was reduced to a great extent.

**Itching or Pruritus**

Ho et al (31) studied the assessment any benefits, compare with a conventional open diathermy technique by Fisher's exact probability test. A total of 119 consecutive patients with prolapsed irreducible hemorrhoids contained 62 conventional open diathermy technique and 57 stapled hemorrhoidectomy. Conventional patients felt more pruritus during defecation ( CNV 27 (43.5%) vs STP 9(15.8%) ; $P < 0.05$).

Sumboonnanonda K. and Lertsithichai P.(33) studied to the assessment the clinical efficacy, compliance and safety of Ginko biloba –Troxerutin – Heptaminol Hce in the treatment of patients with acute hemorrhoidal attacks in Thailand. Patients with acute hemorrhoidal attacks attending the ano-rectal clinic of the Department of Surgery, Ramathibodi Hospital Medical School during September 2000 and November 2001 were enrolled into this prospective clinical study. 22 patients received 4 capsules of Ginko biloba –Troxerutin – Heptaminol Hce each day for 7 days. The result from

analysis with McNemar's chi-squared test was shown that pruritus ani was not significantly changed after treatment.

Gupta PJ.(38) compared an additional method in treating acutely imflammed piles. Ten tablets of trypsin and chymotrypsin (Chymoral forte, Elder Pharmaceuticals India) were powdered and were mixed with 30 g. of heparin (Thrombophobe, German Remedies Ltd, Germany) ointment. 67 patients received ointment treatment with an average hospital stay of 2 days, 22 patients were treated with the conventional method only, using chi-squared test. It was found that there was negligible local pruritus.

**Discharge**

Sumboonnanonda K. and Lertsithichai P.(33) conducted a prospective clinical study on hospital outpatients and studied the effect of Ginko biloba –Troxerutin – Heptaminol Hce for a week in adults (18-70 years old) with acute hemorrhoidal attacks in the ano-rectal clinic of the Department of Surgery, Ramathibodi Hospital Medical School during September 2000 and November 2001. 22 patients received 4 capsules of Ginko biloba – Troxerutin – Heptaminol Hce each day for 7 days, using with McNemar's chi-squared test It was shown that discharge was significantly improved after treatment ($P< 0.05$).

**Treatment**

Cospite M. (39) evaluated of clinical activity and safety of Daflon 500 mg in the treatment of acute hemorrhoids. One hundred patients with a history of hemorrhoidal disease and suffering from an acute hemorrhoidal attack were randomized into two parallel groups and treated with Daflon 500mg* (D500) or placebo (PL) under double-blind conditions. Daflon 500 mg was administered at the dosage of three tablets bid the first four days and two tablets bid the following three days. Overall improvement of symptoms was greater in the D500 group than in the PL group, from D2 up to D7. The clinical severity of proctorrhagia, anal discomfort, pain, and anal discharge diminished in both groups but to a greater extent in the D500 group ($P< 0.001$ for all parameters except proctorrhagia, $P = 0.006$). Inflammation, congestion, edema, and prolapse were more markedly improved in the D500 group than in the PL group.

Duration and severity of the current hemorrhoidal episode, as assessed by patient self-evaluation, were less important in the D500 group as compared with previous episodes.Use of analgesics and topical medications diminished in both groups, with a major reduction in the D500 group from D4 ($P < 0.001$). Acceptability was good in both groups : no patient experienced major side effects.

In summary, treatment with D500 resulted in a quicker and more pronounced relief of signs and symptoms of acute hemorrhoids than with the placebo.

Sumboonnanonda K. and Lertsithichai P.(33) studied to the assessment the clinical efficacy, compliance and safety of Ginko biloba –Troxerutin – Heptaminol Hce in the treatment of patients with acute hemorrhoidal attacks in the ano-rectal clinic of the Department of Surgery, Ramathibodi Hospital Medical School during September 2000 and November 2001. 22 patients received 4 capsules of Ginko biloba – Troxerutin – Heptaminol Hce each day for 7 days. Adverse effects were found in 2 patients: headache in one patient and dizziness in another. Both patients were able to continue taking the medication.

## 2.3 Logistic regression analysis

Before beginning a study of logistic regression it is important to understand that the goal of an analysis using this method is the same as that of any model-building technique used in statistics: to find the best fitting and most parsimonious, yet biologically reasonable model to describe the relationship between an outcome (dependent or response) variable and a set of independent (predictor or explanatory) variables. These independent variables are often called *covariates*. The most common example of modeling, and one assumed to be familiar to the readers of this text, is the usual linear regression model where the outcome variable is assumed to be continuous.

What distinguishes a logistic regression model from the linear regression model is that the outcome variable in logistic regression is binary or dichotomous. This difference between logistic and linear regression is reflected both in the choice of a parametric model and in the assumptions. Once this difference is accounted for, the methods employed in an analysis using logistic regression follow the same general

principles used in linear regression. Thus, the techniques used in linear regression analysis will motivate our approach to logistic regression.

The factors were associated with hemorrhoids using logistic regression analysis were reviewed for presentation in this paper.

Stewart et al.(23) studied the correlation of constipation in an elderly population. The statistical analysis in this study had 3 steps. A Mantel-Haenszel $\chi^2$ test for a relationship between each of the factors and constipation was used in the initial step. In Variables had a significant association with constipation in the initial step were divided into four factor groups, each consisting of similar factors in the second step. Final step a stepwise logistic regression procedure was performed on each group to identify those factors most highly associated with constipation, the criterion used for inclusion in the model was a significance level less than 0.05.

Johanson and Sonnenberg (24) examined the potential risk factors association with hemorrhoids. The statistical analysis in this study had Woolf's method, Mantel-Haenszel test, and multiple logistic regression. Multiple logistic regression analysis was performed to confirm the significance of individual risk factors as well as to control for potential confounding.

Delco and Sonnenberg (25) determined which diagnoses were associated with the occurrence of hemorrhoids using multiple logistic regression. Woolf's method was used to calculate unadjusted odds ratio and its 95 percent confidence interval in the univariate analysis.

Zaheer et al.(26) studied the risk factors for urinary retention after operations for benign anorectal diseases with stepwise logistic regression. The Mantel-Haenszel test was used to determine the statistical significance of the crude relative risk, and 95 percent confidence intervals were calculated. Stepwise logistic regression analysis was used to identify independent risk factors in both groups of patients separately.

To determine factors associated with hemorrhoids, the logistic regression analysis was also used by several studies. For the most study (Stewart et al., Johanson and Sonnenberg, Delco and Sonnenberg, and Zaheer et al.) stepwise approach was used for entering terms into the model, with 0.05 as the limit for accepting and removing newly entered terms. An enter approach was used in only few studies. Accordingly, the enter

approach was used in this study to retain some important factors in a logistic regression.

From reviewed factors associated with hemorrhoids patients found that some factors associated with hemorrhoids patients in this study. The potential factors associated with hemorrhoids patients were occupation and work activity, defecation behavior, ever or recurrent of hemorrhoids, bleeding, pain, discharge, itching, prolapse. All these factors presented in conceptual framework in Figure 1

## Conceptual Framework

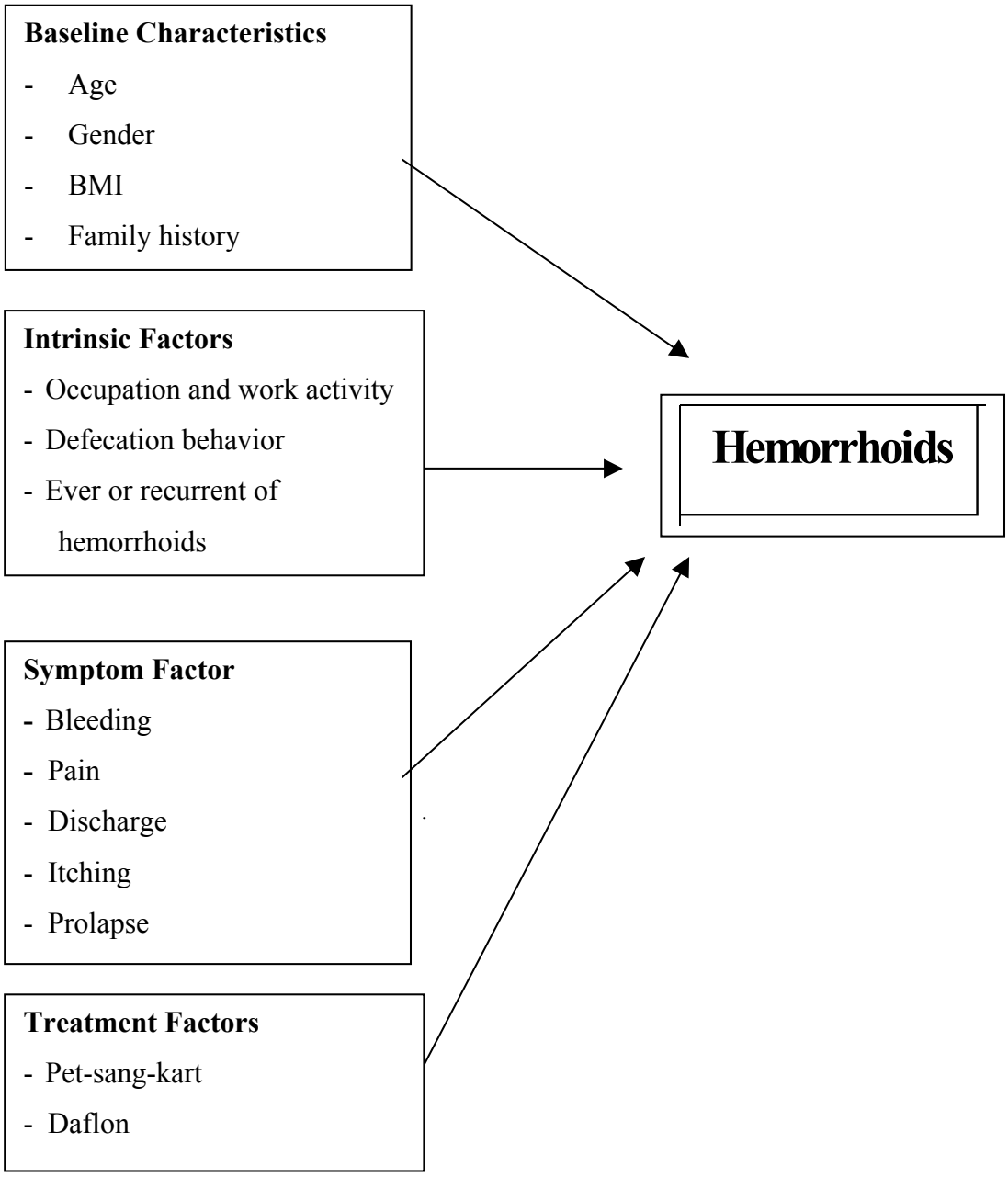


**Figure 1.** Factors associated with hemorrhoids patients

# CHAPTER III
# METHODOLOGY

This study is derived from the clinical trial in the project "Experimental comparative study of the efficacy and side effects of *Cissus quadrangularis L.*; Vitaceae to Daflon 500 mg. (Servier) and placebo in the treatment of acute hemorrhoids".

## 3.1 Source of data

This secondary data were dawn from a phase III clinical trial, comparing effectiveness among *Cissus quadrangularis L.*(Pet-sang-kart), Daflon, and placebo, among outpatients attending general surgery at Rajavithi Hospital, Chonburi Hospital and Sriracha Hospital the period 1st January 2000 and 31st December 2001.

## 3.2 Variables for study

The variables under the study were:

Age group and experience of hemorrhoids (ordinal scale).

Gender, body mass index, family history of hemorrhoids, occupation, type of work activity, defecation behavior, experience of hemorrhoids, recurrent hemorrhoids, bleeding, pain, discharge, itching, prolapse, and severity of hemorrhoids (grade of internal hemorrhoids) which were nominal scale.

According to the study design, there were three sets of treatments: Pet-sang-kart, Daflon 500 mg. and placebo.

## 3.3 Statistical analysis

1. Using frequency distribution percent with age, gender, body mass index, family history of hemorrhoids, occupation, type of work activity, defecation behavior, experience of hemorrhoids, recurrent hemorrhoids, bleeding, pain, discharge, itching, prolapse, and severity of hemorrhoids (grade of internal hemorrhoids).

2. Using univariate analysis to examine the crude association between hemorrhoids and independent factors by chi-square test. Uivariate analysis shows the factors associated with hemorrhoids, by sorting important factors from high to low association.

3. Variables were selected to test a hypothesized association between the two groups in uivariate analysis. A p-value < 0.5 was considered a candidate for logistic regression analysis. Selecting only the important variables from supporting theories and journals were considered in the logistic regression analysis.

4. Logistic regression analysis was used in this study to elicit criteria for including independent variables in the model, concerning the following steps. Method of selection in logistic regression used the enter procedure.

The best model was chosen based on the following criteria:

1. Likelihood ratio, by comparing the likelihood values with and without the independent variable in the equation. It has a distribution that is chi-square with p degree of freedom, under the hypothesis that the coefficients for the variables excluded are equal to zero.

2. The Wald statistic is obtained by comparing the maximum likelihood estimate of the slope parameter, $\beta_1$ , to an estimate of its standard error. The resulting ratio, under the hypothesis that $\beta 1 = 0$, will follow a standard normal distribution. For this test, a significant result indicates a predictor that is reliably associated with hemorrhoids.

3. P-value of Hosmer-Lemeshow proposes a grouping based on the values of the estimated probabilities. The n columns correspond to the n values of the estimated probabilities, with the first column corresponding to the smallest values, and the $n^{th}$ column to the largest value. For the y = 1 row, estimates of the expected values are obtained by summing. The estimated probabilities over all subjects in a group are also calculated. For the y = 0 row, the estimated expected value is obtained by summing, over all subjects in the group, one minus the estimated probability. Goodness of fit is formally evaluated using the Hosmer-Lemeshow statistic where a good model proceduces a non-significant chi-square.

4. Pseudo $R^2$ is a fixed set of possible covariate, higher than p, when the quantity in the denominator of the equation is constant and the numerator is one-half the

likelihood ratio test for the significance of the slope coefficients for the p covariate in the fitted model. Thus, the quantity $R^2$ is nothing more than an expression of the likelihood ratio tests.

**Logistic regression**

The logistic model, the model produce by logistic regression is nonlinear and important reference of the logistic regression analysis concern the nature of the relationship the outcome and more than one independent variable. Then the logit of the multiple logistic regression models is given by

The equation

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3\ldots+\beta pXp$$

Logistic regression emphasizes the probability of the particular out come for each case.

$$P\ (Yj = 1) = e^{(\beta0+\beta1X1)} /[1+ e^{(\beta0+\beta1X1)}]$$

$$1\text{-}P\ (Yj = 1) = 1/[1+ e^{(\beta0+\beta1X1)}]$$

P = Probability of success on an event in the subjects (Y =1)

1-P = Probability of non-success on an event in the subjects (Y =0)

$$P / (1\text{-}P) = \text{Risk ratio}$$

$$P / (1\text{-}P) = e^{(\beta0+\beta1X1)}$$

The transformation is chosen so that the response function is made to be linear, as follows:

$$\text{Ln}\ [\frac{P}{1-P}] = \beta_0 + \beta_1 X_1$$

If $X_i$ for p predictors (i = 1,2,3,…,p) the logistic model equation creates the logit or log of the risk ratio:

$$\text{Ln}\ [\frac{P}{1-P}] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 +\ldots+ \beta_p X_p$$

$X_i$ = independent variables; i = 1,2,3,…,p

$\beta_i$ = coefficient of variable $X_i$ ; i = 1,2,3,…,p

**Assumptions of logistic regression are as follows:** (41,42,43)

1. The binary dependent variable is ln risk ratio which is transformed an equation of

$$P = \frac{e^{(\alpha+\beta_i X_i)}}{1+e^{(\alpha+\beta_i X_i)}}$$

by P = probability of success (y =1) and ln risk ratio is normal distribution.

2. Each variable in explanatory variables is independent from each other.
3. $\varepsilon_i$ and $\varepsilon_j$ uncorrected, $i \neq j$, so that cov ($\varepsilon_i$ , $\varepsilon_j$ ) = 0
4. E ($\varepsilon_i$ , $\varepsilon_j$) = 0
5. E ($\varepsilon_i$ , $X_j$) = 0
6. For any i, $R^2_i$ <1, where $R^2_i$ is the variance in the independent variable $X_i$ that is explained by all of the other independent variables $X_1$, $X_2$, …, $X_{i-1}$, $X_{i+1}$, …, $X_k$. If there is only one predictor, multicollinearity is not an issue.

From $P = \frac{e^{(\alpha+\beta_i X_i)}}{1+e^{(\alpha+\beta_i X_i)}}$ can be written into the equation of treatment

$$P_{X_1=Pet-sang-kart} = \frac{e^{(\alpha+\beta_i X_{Pet-sang-kart})}}{1+e^{(\alpha+\beta_i X_{Pet-sang-kart})}}$$

$$P_{X_2=Daflon} = \frac{e^{(\alpha+\beta_2 X_{Daflon})}}{1+e^{(\alpha+\beta_2 X_{Daflono})}}$$

$$P_{X_3=Placebo} = \frac{e^{(\alpha+\beta_3 X_{Placebo})}}{1+e^{(\alpha+\beta_3 X_{Placebo})}}$$

P is the probability of treatment (Pet-sang-kart, Daflon, and Placebo)

$$RR_{Pet-sang-kart} = \frac{P_{Pet-sang-kart}}{P_{Placebo}}$$

$$RR_{Daflon} = \frac{P_{Daflon}}{P_{Placebo}}$$

### 3.4 Variables for analysis

Then, all variables that used for analysis were 15 variables. These are 13 qualitative variable; gender, body mass index, family history of hemorrhoids, occupation, type of work activity, defecation behavior, recurrent hemorrhoids, bleeding, pain, discharge, itching, prolapse, and severity of hemorrhoids (grade of internal hemorrhoids) and 2 quantitative variable; age, experience of hemorrhoids (Table 1).

**Table 1.** Binary coding for dummy variables of the category data

| Category variables | Dummy variables |
|---|---|
| **Dependent variable** | |
| **Improvement hemorrhoids** | X1 |
| Yes | 1 |
| No* | 0 |
| *Baseline characteristics* | |
| **Age** | X2 X3 |
| ≥ 40 years | 1 0 |
| 25 – 39 years | 0 1 |
| ≤ 24 years* | 0 0 |
| **Gender** | X4 |
| Male | 1 |
| Female* | 0 |
| **Body mass index** | X5 |
| ≥ 25 kg/$m^2$ | 1 |
| < 25 kg/$m^2$ * | 0 |
| **Family history of hemorrhoids** | X6 |
| Yes | 1 |
| No* | 0 |

* Reference category

**Table 1.** Binary coding for dummy variables of the category data (continued)

| Category variables | Dummy variables |
|---|---|
| *Intrinsic factors* | |
| **Occupation** | X7 X8 X9 |
| Labor work | 1 0 0 |
| Merchandise | 0 1 0 |
| Civil service | 0 0 1 |
| No job | 0 0 0 |
| **Type of work activity** | X10 X11 |
| Heavy lifting | 1 0 |
| Daily standing | 0 1 |
| Regular | 0 0 |
| **Defecation behavior** | X12 X13 |
| Constipation | 1 0 |
| Diarrhea | 0 1 |
| Normal | 0 0 |
| **Experience of hemorrhoids** | X14 X15 |
| ≥ 2 times | 1 0 |
| 1 time | 0 1 |
| No | 0 0 |
| **Recurrent hemorrhoids** | X16 X17 X18 |
| Constipation | 1 0 0 |
| Diarrhea | 0 1 0 |
| After alcohol drinking/ hot food | 0 0 1 |
| Not specify | 0 0 0 |

**Table 1.** Binary coding for dummy variables of the category data (continued)

| Category variables | Dummy variables | | |
|---|---|---|---|
| *Intrinsic factors* | | | |
| **Recurrent hemorrhoids** | X16 | X17 | X18 |
| Constipation | 1 | 0 | 0 |
| Diarrhea | 0 | 1 | 0 |
| After alcohol drinking/ hot food | 0 | 0 | 1 |
| Not specify | 0 | 0 | 0 |
| *Symptom of factors* | | | |
| **Bleeding** | X19 | X20 | X21 |
| Severe | 1 | 0 | 0 |
| Moderate | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 |
| No* | 0 | 0 | 0 |
| **Pain** | X22 | X23 | X24 |
| Severe | 1 | 0 | 0 |
| Moderate | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 |
| No* | 0 | 0 | 0 |
| **Discharge** | X25 | X26 | X27 |
| Severe | 1 | 0 | 0 |
| Moderate | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 |
| No* | 0 | 0 | 0 |
| **Itching** | X28 | X29 | X30 |
| Severe | 1 | 0 | 0 |
| Moderate | 0 | 1 | 0 |
| Mild | 0 | 0 | 1 |
| No* | 0 | 0 | 0 |

**Table 1.** Binary coding for dummy variables of the category data (continued)

| Category variables | Dummy variables | | |
|---|---|---|---|
| *Symptom of factors* | | | |
| **Prolapse** | X31 | X32 | X33 |
| Unable to be reduced | 1 | 0 | 0 |
| Requiring manual reduction | 0 | 1 | 0 |
| But reduce spontaneously | 0 | 0 | 1 |
| No prolapse* | 0 | 0 | 0 |
| **Severity of hemorrhoids** | | | |
| **(grade of internal hemorrhoids)** | X34 | X35 | |
| Severe | 1 | 0 | |
| Moderate | 0 | 1 | |
| Mild* | 0 | 0 | |
| **Treatment Factors** | X36 | X37 | |
| Pet-sang-kart | 1 | 0 | |
| Daflon | 0 | 1 | |
| Placebo* | 0 | 0 | |

# CHAPTER IV
# RESULTS

This research design was a phase III clinical trial to comparing the effectiveness of *Cissus quadrangularis* L.(Pet-sang-kart)**,** Daflon and placebo among outpatients attending general surgery at Rajavithi, Chonburi and Sriracha hospitals during the period 1st January 2000 and 31st December 2001. The data consisted of 526 patients with acute hemorrhoids. Accordingly, the results for 526 patients are presented, as follows:

1. General characteristics of the patients
2. The crude analysis of each factor, comparing improvement and no improvement in hemorrhoids after treatment
3. Logistic regression for model selection

## 4.1 General characteristics of the patients

The study sample selected was 572 patients with acute hemorrhoids, consisting of 234 patients from Rajavithi Hospital, 240 from Chonburi Hospital, and 98 from Sriracha Hospital. As some were lost to follow-up, the study retained 526 patients, consisting of 223 from Rajavithi Hospital, 212 from Chonburi Hospital, and 91 from Sriracha Hospital. There were only 91 patients from Sriracha Hospital, compared with 223 and 212 from the other hospitals, due to clinical data management problems.

The baseline characteristics of the patients were considered by hospital site. There were no significant differences in baseline characteristics for age, gender, body mass index, or family history of hemorrhoids, with p-values of 0.622, 0.596, 0.310 and 0.443, respectively. Three hospitals had similar baseline characteristics, so that the distributions of data were not different. About 50% of the patients in the three hospitals were 25-39 years of age. The mean age of the patients was about 35 years. Almost 80% of the patients had a body mass index in the normal range, and more than half had no family history of hemorrhoids.

Patient intrinsic factors consisted of occupation type, type of work activity, defecation behavior, experience with hemorrhoids, and recurrent hemorrhoids. There were highly significant differences between the three hospitals (p-value < 0.001). Most the patients were laborers (about 59, 45, and 70%, respectively). The minority of patients were civil servants (6.3 and 14.2%), in Rajavithi and Chonburi hospitals, respectively. About 70% of patients in the three hospitals were regular workers. Most of the patients had symptoms of constipation (47 and 74.5%) in Rajavithi and Chonburi hospitals. A minority of the patients had diarrhea (9.4, 3.3, and 11.0%) in these three hospitals, respectively. Single experience of hemorrhoids was 69.8% in Chonburi Hospital, while multiple experiences were 47.5 and 46% in Rajavithi and Sriracha hospitals, respectively. Almost 80% were constipated with recurrent hemorrhoids in Chonburi Hospital and about 40% in Rajavithi and Sriracha hospitals.

Hemorrhoidal symptoms were highly significantly different in the three hospitals (bleeding, pain, discharge, and prolapse; p-value < 0.001). The numbers of patient with bleeding were moderate (62.8, 43.9, and 61.5%) in the three hospitals, respectively. Half of the patients had no pain (58.3 and 44.0%) in Rajavithi and Sriracha hospitals, respectively. Most patients had no discharge or itching (about 80 and 65%) in the three hospitals. Patients did not have prolapse in the three hospitals at rates of about 44, 29, and 45%, respectively. Patients were examined by proctoscopy before treatment, and the majority were moderate hemorrhoid cases in Rajavithi and Sriracha hospitals (Table 2).

The 526 patients with acute hemorrhoids consisted of 174 patients receiving Pet-sang-kart, 174 patients receiving Daflon, and 178 patients receiving placebo.

Baseline characteristics of the patients were considered by treatment. There were no significant differences in baseline characteristics for age, gender, body mass index, or family history of hemorrhoids. Three treatments had similar baseline characteristics, so that the distribution of data was similar; in addition, the patients had been allocated at random. Half of the patients were females receiving Daflon and placebo (54%).

The intrinsic factors of the patients consisted of occupation type, type of work activity, defecation behavior, experience of hemorrhoids, and recurrent hemorrhoids. These were similar for the three treatments. Most patients were laborers, and received Pet-sang-kart, Daflon and placebo (45.5, 58.6, and 61.8%, respectively). In the three

treatment groups, 43% of the patients had a single experience of hemorrhoids, while 56.6% were constipated with recurrent of hemorrhoids.

Hemorrhoidal symptoms were similar in the three treatments. More than half of patients in the three treatments had moderate bleeding. Almost 80% had no discharge. The rate of no prolapse in the three treatments was 36.8, 40.8 and 37.1%, repectively). The patients were examined with proctoscopy before treatment; the majority (50%) were moderate hemorrhoid cases who received Pet-sang-kart and Daflon (Table 3).

**Table 2.** General characteristics of the patients by hospital site, n = 526

| Characteristics | Site | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Rajavithi hospital | | Chonburi hospital | | Sriracha hospital | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| *Baseline characteristics* | | | | | | | |
| **Age** | | | | | | | >0.05 |
| ≥ 40 years | 68 | 30.5 | 78 | 36.8 | 31 | 34.1 | |
| 25 – 39 years | 114 | 51.1 | 104 | 49.1 | 46 | 50.5 | |
| ≤ 24 years | 41 | 18.4 | 30 | 14.2 | 14 | 15.4 | |
| **Gender** | | | | | | | >0.05 |
| Male | 102 | 45.7 | 104 | 49.1 | 47 | 51.6 | |
| Female | 121 | 54.3 | 108 | 50.9 | 44 | 48.4 | |
| **Body mass index** | | | | | | | >0.05 |
| ≥ 25 $kg/m^2$ | 49 | 22.0 | 38 | 17.9 | 23 | 25.3 | |
| < 25 $kg/m^2$ | 174 | 78.0 | 174 | 82.1 | 68 | 74.7 | |
| **Family history of hemorrhoids** | | | | | | | >0.05 |
| Yes | 109 | 48.9 | 92 | 43.4 | 45 | 49.5 | |
| No | 114 | 51.1 | 120 | 56.6 | 46 | 50.5 | |
| *Intrinsic factors* | | | | | | | |
| **Occupation** | | | | | | | 0.001 |
| Labor work | 132 | 59.2 | 95 | 44.8 | 64 | 70.3 | |
| Merchandise | 38 | 17.0 | 48 | 22.6 | 11 | 12.1 | |
| Civil service | 14 | 6.3 | 30 | 14.2 | 4 | 4.4 | |
| No job | 39 | 17.5 | 39 | 18.4 | 12 | 13.2 | |
| **Type of work activity** | | | | | | | 0.014 |
| Heavy lifting | 34 | 15.2 | 45 | 21.2 | 19 | 20.9 | |
| Daily standing | 28 | 12.6 | 10 | 4.7 | 13 | 14.3 | |
| Regular | 161 | 72.2 | 157 | 74.1 | 59 | 64.8 | |

$n_1$ is the number of patients from Rajavithi hospital
$n_2$ is the number of patients from Chonburi hospital
$n_3$ is the number of patients from Sriracha hospital

**Table 2.** General characteristics of the patients by hospital site, n = 526 (continued)

| Characteristics | Site | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Rajavithi hospital | | Chonburi hospital | | Sriracha hospital | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| *Intrinsic factors* | | | | | | | |
| **Defecation behavior** | | | | | | | <0.001 |
| Constipation | 105 | 47.1 | 158 | 74.5 | 42 | 46.1 | |
| Diarrhea | 21 | 9.4 | 7 | 3.3 | 10 | 11.0 | |
| Normal | 97 | 43.5 | 47 | 22.2 | 39 | 42.9 | |
| **Experience of hemorrhoids** | | | | | | | <0.001 |
| ≥ 2 times | 106 | 47.5 | 1 | 0.5 | 42 | 46.1 | |
| 1 time | 49 | 22.0 | 148 | 69.8 | 28 | 30.8 | |
| No | 68 | 30.5 | 63 | 29.7 | 21 | 23.1 | |
| **Recurrent hemorrhoids** | | | | | | | <0.001 |
| Constipation | 89 | 39.9 | 176 | 83.0 | 33 | 36.2 | |
| Diarrhea | 21 | 9.4 | 7 | 3.3 | 7 | 7.7 | |
| After alcohol drinking/ hot food | 44 | 19.7 | 24 | 11.3 | 17 | 18.7 | |
| Not specify | 69 | 31.0 | 5 | 2.4 | 34 | 37.4 | |
| *Symptom of factors* | | | | | | | |
| **Bleeding** | | | | | | | <0.001 |
| Severe | 64 | 28.7 | 33 | 15.5 | 25 | 27.5 | |
| Moderate | 140 | 62.8 | 93 | 43.9 | 56 | 61.5 | |
| Mild | 15 | 6.7 | 29 | 13.7 | 8 | 8.8 | |
| No | 4 | 1.8 | 57 | 27.9 | 2 | 2.2 | |
| **Pain** | | | | | | | <0.001 |
| Severe | 11 | 4.9 | 36 | 17.0 | 6 | 6.5 | |
| Moderate | 38 | 17.1 | 76 | 35.8 | 18 | 19.8 | |
| Mild | 44 | 19.7 | 40 | 18.9 | 27 | 29.7 | |
| No | 130 | 58.3 | 60 | 28.3 | 40 | 44.0 | |

**Table 2.** General characteristics of the patients by hospital site, n = 526 (continued)

| Characteristics | Site | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Rajavithi hospital | | Chonburi hospital | | Sriracha hospital | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| **Discharge** | | | | | | | <0.001 |
| Severe | 6 | 2.7 | 0 | 0.0 | 1 | 1.1 | |
| Moderate | 14 | 6.3 | 6 | 2.8 | 7 | 7.7 | |
| Mild | 33 | 14.8 | 4 | 1.9 | 18 | 19.8 | |
| No | 170 | 76.2 | 202 | 95.3 | 65 | 71.4 | |
| **Itching** | | | | | | | >0.05 |
| Severe | 8 | 3.6 | 2 | 0.9 | 3 | 3.3 | |
| Moderate | 12 | 5.4 | 18 | 8.5 | 7 | 7.7 | |
| Mild | 53 | 23.8 | 49 | 23.1 | 26 | 28.6 | |
| No | 150 | 67.2 | 143 | 67.5 | 55 | 60.4 | |
| **Prolapse** | | | | | | | <0.001 |
| Unable to be reduced | 10 | 4.5 | 26 | 12.3 | 6 | 6.5 | |
| Requiring manual reduction | 36 | 16.1 | 58 | 27.4 | 15 | 16.5 | |
| But reduce spontaneously | 79 | 35.5 | 66 | 31.1 | 29 | 31.9 | |
| No prolapse | 98 | 43.9 | 62 | 29.2 | 41 | 45.1 | |
| **Severity of hemorrhoids** | | | | | | | >0.05 |
| Severe | 30 | 13.5 | 35 | 16.5 | 15 | 16.5 | |
| Moderate | 105 | 47.0 | 86 | 40.6 | 51 | 56.0 | |
| Mild | 88 | 39.5 | 91 | 42.9 | 27 | 27.5 | |

**Table 3.** General characteristics of the patients by treatment, n = 526

| Characteristics | Treatment | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Pet-sang-kart | | Daflon | | Placebo | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| *Baseline characteristics* | | | | | | | |
| **Age** | | | | | | | >0.05 |
| ≥ 40 years | 67 | 38.5 | 57 | 32.8 | 53 | 29.8 | |
| 25 – 39 years | 77 | 44.3 | 86 | 49.4 | 101 | 56.7 | |
| ≤ 24 years | 30 | 17.2 | 31 | 17.8 | 24 | 13.5 | |
| **Gender** | | | | | | | >0.05 |
| Male | 91 | 52.3 | 80 | 46.0 | 82 | 46.1 | |
| Female | 83 | 47.7 | 94 | 54.0 | 96 | 53.9 | |
| **Body mass index** | | | | | | | >0.05 |
| ≥ 25 kg/m$^2$ | 34 | 19.5 | 32 | 18.4 | 44 | 24.7 | |
| < 25 kg/m$^2$ | 140 | 80.5 | 142 | 81.6 | 134 | 75.3 | |
| **Family history of hemorrhoids** | | | | | | | >0.05 |
| Yes | 80 | 46.0 | 83 | 47.7 | 83 | 46.6 | |
| No | 94 | 54.0 | 91 | 52.3 | 95 | 53.4 | |
| *Intrinsic factors* | | | | | | | |
| **Occupation type** | | | | | | | 0.010 |
| Labor work | 79 | 45.5 | 102 | 58.6 | 110 | 61.8 | |
| Merchandise | 46 | 26.4 | 30 | 17.3 | 21 | 11.8 | |
| Civil service | 15 | 8.6 | 14 | 8.0 | 19 | 10.7 | |
| No job | 34 | 19.5 | 28 | 16.1 | 28 | 15.7 | |
| **Type of work activity** | | | | | | | >0.05 |
| Heavy lifting | 26 | 15.0 | 34 | 19.5 | 38 | 21.3 | |
| Daily standing | 19 | 10.9 | 13 | 7.5 | 19 | 10.7 | |
| Regular | 129 | 74.1 | 127 | 73.0 | 121 | 68.0 | |

$n_1$ is the number of patients from Rajavithi hospital
$n_2$ is the number of patients from Chonburi hospital
$n_3$ is the number of patients from Sriracha hospital

**Table 3.** General characteristics of the patients by treatment, n = 526 (continued)

| Characteristics | Treatment | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Pet-sang-kart | | Daflon | | Placebo | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| **Defecation behavior** | | | | | | | >0.05 |
| Constipation | 98 | 56.3 | 107 | 61.5 | 100 | 56.2 | |
| Diarrhea | 10 | 5.7 | 14 | 8.0 | 14 | 7.8 | |
| Normal | 68 | 38.0 | 53 | 30.5 | 64 | 36.0 | |
| **Experience of hemorrhoids** | | | | | | | >0.05 |
| ≥ 2 times | 55 | 31.6 | 48 | 27.6 | 46 | 25.8 | |
| 1 time | 74 | 42.5 | 70 | 40.2 | 81 | 45.5 | |
| No | 45 | 25.9 | 56 | 32.2 | 51 | 28.7 | |
| **Recurrent hemorrhoids** | | | | | | | >0.05 |
| Constipation | 101 | 58.1 | 96 | 55.1 | 101 | 56.7 | |
| Diarrhea | 5 | 2.9 | 12 | 6.9 | 18 | 10.1 | |
| After alcohol drinking/hot food | 30 | 17.2 | 25 | 14.4 | 30 | 16.9 | |
| Not specify | 38 | 21.8 | 41 | 23.6 | 29 | 16.3 | |
| *Symptom factors* | | | | | | | |
| **Bleeding** | | | | | | | >0.05 |
| Severe | 47 | 27.0 | 40 | 23.0 | 35 | 19.7 | |
| Moderate | 91 | 52.4 | 93 | 53.4 | 105 | 59.0 | |
| Mild | 18 | 10.3 | 21 | 12.1 | 13 | 7.3 | |
| No | 18 | 10.3 | 20 | 11.5 | 25 | 14.0 | |
| **Pain** | | | | | | | >0.05 |
| Severe | 26 | 14.9 | 13 | 7.4 | 14 | 7.9 | |
| Moderate | 35 | 20.1 | 47 | 27.0 | 50 | 28.1 | |
| Mild | 35 | 20.1 | 37 | 21.3 | 39 | 21.9 | |
| No | 78 | 44.9 | 77 | 44.3 | 75 | 42.1 | |

**Table 3.** General characteristics of the patients by treatment, n = 526 (continued)

| Characteristics | Treatment | | | | | | p-value |
|---|---|---|---|---|---|---|---|
| | Pet-sang-kart | | Daflon | | Placebo | | |
| | $n_1$ | (%) | $n_2$ | (%) | $n_3$ | (%) | |
| **Discharge** | | | | | | | >0.05 |
| Severe | 3 | 1.7 | 3 | 1.7 | 1 | 0.6 | |
| Moderate | 8 | 4.6 | 9 | 5.2 | 10 | 5.6 | |
| Mild | 16 | 9.2 | 21 | 12.1 | 18 | 10.1 | |
| No | 147 | 84.5 | 141 | 81.0 | 149 | 83.7 | |
| **Itching** | | | | | | | >0.05 |
| Severe | 4 | 2.3 | 4 | 2.3 | 5 | 2.8 | |
| Moderate | 13 | 7.5 | 11 | 6.3 | 14 | 7.3 | |
| Mild | 34 | 19.5 | 47 | 27.0 | 49 | 26.4 | |
| No | 123 | 70.7 | 112 | 64.4 | 122 | 63.5 | |
| **Prolapse** | | | | | | | >0.05 |
| Unable to be reduced | 14 | 8.0 | 12 | 6.9 | 16 | 9.0 | |
| Requiring manual reduction | 34 | 19.6 | 34 | 19.5 | 41 | 23.0 | |
| But reduce spontaneously | 62 | 35.6 | 57 | 32.8 | 55 | 30.9 | |
| No prolapse | 64 | 36.8 | 71 | 40.8 | 66 | 37.1 | |
| **Severity of hemorrhoids** | | | | | | | 0.032 |
| Severe | 23 | 13.2 | 20 | 11.5 | 37 | 20.8 | |
| Moderate | 82 | 47.1 | 92 | 52.9 | 68 | 38.2 | |
| Mild | 69 | 39.7 | 62 | 35.6 | 73 | 41.0 | |

## 4.2 Crude analysis of each factor, comparing improvement and no improvement in hemorrhoids after treatment

The patients in this study had improved hemorrhoids after treatment. Half of the patients (51.9%) were 25-39 years of age. More than half of the patients (55.8%) were male and 53.8% had no family history of hemorrhoids. About 75% of patients had a body mass index in the normal range. More than half of patients with improved hemorrhoids were laborers (57.7%) and the daily work of 4% of patients with improved hemorrhoids involved standing. After treatment, the patients with diarrhea (36.84%) improved. About 12.44% of patients had hemorrhoids more than once, and 11.41% of patients were constipated, and after treatment the patients with hemorrhoids improved. Most of the patients had no or mild hemorrhoidal symptoms (pain, discharge, itching, and prolapse). After treatment, bleeding, pain, discharge, itching, and prolapse were not significantly improved. About 33.75% of patients had severe hemorrhoids; after treatment, the patients with severe hemorrhoids significantly improved.

The factors associated with hemorrhoids were considered in relation to the severity of hemorrhoids after treatment. The chi-square test was used to test against the null hypothesis that selected factors are independent of hemorrhoids after treatment, as shown in Table 4. All test results with p-value $< 0.05$ were considered as having a lower chance of support for the null hypothesis. Defecation behavior and severity of hemorrhoids before treatment were analyzed to determine the effects on hemorrhoids after treatment.

**Table 4.** The association between factors with hemorrhoids after treatment

| Factors | Hemorrhoids after treatment | | | | P-value |
|---|---|---|---|---|---|
| | Improve | | Not improve | | |
| | $n_1$ | (%) | $n_2$ | (%) | |
| | 52 | | 474 | | |
| *Baseline characteristics* | | | | | |
| **Age** | | | | | 0.965 |
| ≥ 40 years | 17 | 32.7 | 160 | 33.8 | |
| 25 – 39 years | 27 | 51.9 | 237 | 50.0 | |
| ≤ 24 years | 8 | 15.4 | 77 | 16.2 | |
| **Gender** | | | | | 0.244 |
| Male | 29 | 55.8 | 224 | 47.3 | |
| Female | 23 | 44.2 | 250 | 52.7 | |
| **Body mass index** | | | | | 0.445 |
| ≥ 25 $kg/m^2$ | 13 | 25.0 | 97 | 20.5 | |
| < 25 $kg/m^2$ | 39 | 75.0 | 377 | 79.5 | |
| **Family history of hemorrhoids** | | | | | 0.925 |
| Yes | 24 | 46.2 | 222 | 46.8 | |
| No | 28 | 53.8 | 252 | 53.2 | |
| *Intrinsic factors* | | | | | |
| **Occupation type** | | | | | 0.411 |
| Labor work | 30 | 57.7 | 261 | 55.0 | |
| Mercantile | 6 | 11.5 | 91 | 19.2 | |
| Civil service | 4 | 7.7 | 44 | 9.3 | |
| No job | 12 | 23.1 | 78 | 16.5 | |

**Table 4.** The association between factors with hemorrhoids after treatment (continued)

| Factors | Hemorrhoids after treatment | | | | P-value |
|---|---|---|---|---|---|
| | Improve | | Not improve | | |
| | $n_1$ | (%) | $n_2$ | (%) | |
| | 52 | | 474 | | |
| *Intrinsic factors* | | | | | |
| **Type of work activity** | 6 | 11.6 | 92 | 19.4 | 0.084 |
| Heavy lifting | 2 | 3.8 | 49 | 10.3 | |
| Daily standing | 44 | 84.6 | 333 | 70.3 | |
| Regular | | | | | |
| **Defecation behavior** | | | | | <0.001* |
| Constipation | 23 | 44.3 | 282 | 59.5 | |
| Diarrhea | 14 | 26.9 | 24 | 5.1 | |
| Normal | 15 | 28.8 | 168 | 35.4 | |
| **Experience of hemorrhoids** | | | | | 0.077 |
| ≥ 2 times | 28 | 53.8 | 197 | 41.6 | |
| 1 times | 16 | 30.8 | 136 | 28.7 | |
| No | 8 | 15.4 | 141 | 29.7 | |
| **Recurrent hemorrhoids** | | | | | 0.518 |
| Constipation | 34 | 65.5 | 264 | 55.7 | |
| Diarrhea | 2 | 3.8 | 33 | 7.0 | |
| After alcohol drinking /hot food | 6 | 11.5 | 79 | 16.7 | |
| Not specify | 10 | 19.2 | 98 | 20.7 | |
| *Symptom factors* | | | | | |
| **Bleeding** | | | | | 0.948 |
| Severe | 13 | 25.0 | 109 | 23.0 | |
| Moderate | 29 | 55.8 | 260 | 54.9 | |
| Mild | 5 | 9.6 | 47 | 9.9 | |
| No | 5 | 9.6 | 58 | 12.2 | |

* Significant with p-value less than 0.05

**Table 4.** The association between factors with hemorrhoids after treatment (continued)

| Factors | Hemorrhoids after treatment | | | | P-value |
|---|---|---|---|---|---|
| | Improve | | Not improve | | |
| | $n_1$ | (%) | $n_2$ | (%) | |
| | 52 | | 474 | | |
| *Symptom factors* | | | | | |
| **Pain** | | | | | 0.933 |
| Severe | 4 | 7.7 | 49 | 10.3 | |
| Moderate | 13 | 25.0 | 119 | 25.1 | |
| Mild | 12 | 23.1 | 99 | 20.9 | |
| No | 23 | 44.2 | 207 | 43.7 | |
| **Discharge** | | | | | 0.285 |
| Severe | 0 | 0 | 7 | 1.5 | |
| Moderate | 5 | 9.6 | 22 | 4.6 | |
| Mild | 7 | 13.5 | 48 | 10.1 | |
| No | 40 | 76.9 | 397 | 83.8 | |
| **Itching** | | | | | 0.707 |
| Severe | 1 | 1.9 | 12 | 2.5 | |
| Moderate | 2 | 3.8 | 35 | 7.4 | |
| Mild | 15 | 28.8 | 113 | 23.8 | |
| No | 34 | 65.5 | 314 | 66.2 | |
| **Prolapse** | | | | | 0.345 |
| Unable to be reduced | 3 | 5.8 | 39 | 8.2 | |
| Requiring manual reduction | 12 | 23.1 | 97 | 20.5 | |
| But reduce spontaneously | 22 | 42.3 | 152 | 32.1 | |
| No prolapse | 15 | 28.8 | 186 | 39.2 | |

**Table 4.** The association between factors with hemorrhoids after treatment (continued)

| Factors | Hemorrhoids after treatment | | | | P-value |
|---|---|---|---|---|---|
| | Improve | | Not improve | | |
| | $n_1$ | (%) | $n_2$ | (%) | |
| | 52 | | 474 | | |
| **Severity of hemorrhoids** | | | | | <0.001* |
| Severe | 27 | 51.9 | 53 | 11.2 | |
| Moderate | 25 | 48.1 | 217 | 45.8 | |
| Mild | 0 | 0 | 204 | 43.0 | |
| *Treatment Factors* | | | | | 0.767 |
| Pet-sang-kart | 19 | 36.6 | 155 | 32.7 | |
| Daflon | 15 | 28.8 | 159 | 33.5 | |
| Placebo | 18 | 34.6 | 160 | 33.8 | |

### 4.3 Using logistic regression for model selection

To study the factors associated with hemorrhoids after treatment, unconditional logistic regression was applied the method of selection, and logistic regression used the enter procedure. The criteria included independent variables into the model concerning the following step.

Hosmer and Lemeshow ’s guide, in their textbook on applied logistic regression, stated that variables selected as candidates for multivariate analysis should be screened form bivariate analysis with p-value less than 0.20. In addition, these variables were selected from biologically importance sources. Base on these criteria, only 4 variables were left in the multivariate analysis--type of work activity, defecation behavior, experience of hemorrhoids, and severity of hemorrhoids. Since main interest was treatment and the severity of hemorrhoids was known, and because there may be some interaction with the treatment, treatments were force in the model. Four models seemed to be good fit. Table 5 showed four models, as follows:

Model 0 was the initiate constant model with no variable. Next, model 1 started to include four of five variables identified in the crude analysis entered into the model. After that, each variable in model 1 was removed and refitted. It appeared that model excluding defecation behavior, which was model 2, was better than model 1. By the same verifying technique, work activity and experience of hemorrhoids were removed for model 3. At last, two variables containing in model 3 were the severity of hemorrhoids and treatment.

In model 0, the value of the log-likelihood ratio that contained only the constant was 339.343. Model 1 entered five variables was found that four variables were significant. The p-value of Hosmer-Lemeshow was 0.502, likelihood ratio was 250.64 and pseudo $R^2$ 15.5. In Model 2, defecation behavior was eliminated from the model. The likelihood ratio was 255.140, pseudo $R^2$ 14.8 and p-value for goodness of fit was 0.541, better than in model 1. In model 3, type of work activity and experience of hemorrhoids were removed. The p-value of Hosmer-Lemeshow was 0.465, likelihood ratio was 268.839 and closed to model 2, and pseudo $R^2$ was 12.5. Model 3 had minimized the number of variables in the model as the resultant model was more likely to be numerically stable, and was more easily generalized. Therefore the best model was model 3. This implies that model 3 contained severity of hemorrhoids, treatment ( Pet-sang-kart and Daflon), and interaction of severity of hemorrhoids with treatment use were appropriate to explain treatment for curing hemorrhoids with goodness of fit test having a p-value of 0.465 and pseudo $R^2$ of 12.5% (Table 5).

**Table 5.** Coefficients of the selected variables in multiple logistic regression patients with hemorrhoids

| Model | Constant | Severity of hemorrhoids (grade) | Pet-sang-kart | Daflon | Proc * Pet-sang-kart | Proc* Daflon | Work activity | Defecation | Experience hemorrhoids | -2LL | p-value of Hosmer-Lemeshow | Pseudo $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | -2.21* | | | | | | | | | 339.343 | | |
| 1 | 0.41 | -2.00* | 1.23 | 0.26 | -0.52 | -0.09 | 0.59* | 0.40* | -0.64* | 250.640 | 0.502 | 15.5 |
| 2 | 0.80 | -1.88* | 1.09 | 0.17 | -0.46 | -0.07 | 0.62* | | -0.60* | 255.140 | 0.541 | 14.8 |
| 3 | 1.05 | -1.78* | 1.00 | 0.11 | -0.39 | -0.02 | | | | 268.839 | 0.465 | 12.5 |

* Significant with p-value less than 0.05

The result of multivariate analysis to building fit model is given by

$$\text{Ln}\ [\frac{P}{1-P}] = \beta_0 + \beta_1 X_{34} + \beta_2 X_{35} + \beta_3 X_{36} + \beta_4 X_{34} X_{35} + \beta_5 X_{34} X_{36}$$

Severity of hemorrhoids = $X_{34}$

Pet-sang-kart = $X_{35} = 1,\ X_{36} = 0$

Daflon = $X_{35} = 0,\ X_{36} = 1$

Placebo = $X_{35} = 0,\ X_{36} = 0$

The logistic model for predicting hemorrhoids is shown as follow:

$$\text{Ln}\ [\frac{P}{1-P}] = 1.05 - 1.78\ X_{34} + 1.00\ X_{35} + 0.11\ X_{36} - 0.39\ X_{34} X_{35} - 0.02\ X_{34} X_{36}$$

From logistic model for predicting is $\text{Ln}\ [\frac{P}{1-P}]$ which can be transformed in to the equation of

$$P = \frac{e^{(\alpha + \beta_i X_i)}}{1 + e^{(\alpha + \beta_i X_i)}}$$

P is the probability of improvement

$$P_{x35=\text{Pet-sang-kart}} = \frac{e^{(\alpha + \beta_1 X_{34} + \beta_2 (1) + \beta_4 X_{34} (1))}}{1 + e^{(\alpha + \beta_1 X_{34} + \beta_2 (1) + \beta_4 X_{34} (1))}}$$

$$P_{x35=\text{Placebo}} = \frac{e^{(\alpha + \beta_1 X_{34} + \beta_2 (0) + \beta_4 X_{34} (0))}}{1 + e^{(\alpha + \beta_1 X_{34} + \beta_2 (0) + \beta_4 X_{34} (0))}}$$

$$P_{x36=Daflon} = \frac{e^{(\alpha+\beta_1 X_{34}+\beta_3(1)+\beta_5 X_{34}(1))}}{1+e^{(\alpha+\beta_1 X_{34}+\beta_3(1)+\beta_5 X_{34}(1))}}$$

$$P_{x36=Placebo} = \frac{e^{(\alpha+\beta_1 X_{34}+\beta_3(1)+\beta_5 X_{34}(1))}}{1+e^{(\alpha+\beta_1 X_{34}+\beta_3(1)+\beta_5 X_{34}(1))}}$$

$$RR_1 = \frac{P_{Pet-sang-kart}}{P_{Placebo}}$$

$$RR_2 = \frac{P_{Daflon}}{P_{Placebo}}$$

**Table 6.** Estimated relative ratio of improvement among three treatments after adjusted for disease severity

| Severity | Treatment | Improvement | | RR (95% CI) |
|---|---|---|---|---|
| | | Yes | No | |
| Mild | Pet-sang-kart | - | 69 | NA |
| | Daflon | - | 62 | |
| | Placebo | - | 73 | |
| Moderate | Pet-sang-kart | 9 | 73 | 1.07 (0.42 – 2.71) |
| | Daflon | 9 | 83 | 0.95 (0.37 – 2.43) |
| | Placebo | 7 | 61 | 1 |
| Severe | Pet-sang-kart | 10 | 13 | 1.46 (0.74 – 2.89) |
| | Daflon | 6 | 14 | 1.00 (0.44 – 2.32) |
| | Placebo | 11 | 26 | 1 |

NA = Not applicable

Unconditional logistic regression was performed and the risk ratio among treatments were estimated. After taking severity into account, the risk ratio of Pet-sang-kart compared with the placebo was 1.07, while the risk ratio for Daflon compared with placebo was 0.95. It may be interpreted that, among the hemorrhoids patients of moderate condition, the risk ratios were similar. For the severe group, the comparative risk ratio between Pet-sang-kart and placebo was 1.46, showing that patients who received Pet-sang-kart would have 1.46 times greater improvement in severe hemorrhoids than those receiving a placebo. A lower risk ratio was found between Daflon and placebo, at 1.00, meaning that the patients with moderate hemorrhoids who received Daflon did not improve differently from those who received the placebo.

# CHAPTER V
# DISCUSSION

## Results of the study

Of all 526 patients with hemorrhoids, only 52 improved (about 9.89%). Twenty-seven patients with hemorrhoids were severe (about 33.75%), and after treatment the severity significantly improved (p-value < 0.001). Twenty-five patients with moderate hemorrhoids (about 10.33%) did not experience significant change in severity after treatment. Therefore, patients with severe hemorrhoids should be included in this study, since after treatment they had obviously improved. The numbers of patients with moderate or severe hemorrhoids were increased in this study because they showed the greatest improvement with treatment. Patients with highly severe hemorrhoids were not included in this study.

No drug effects could be found in the mild hemorrhoid cases. No patients with mild hemorrhoids were found in the improvement data cells. This meant that only patients in the moderate or severe groups should be recruited. The risk ratio could not be estimated, because there was no marginal total for improvement in the mild group. Comparative assessment of the moderate and severe groups with drug treatment showed interaction.

The study results revealed the effect of the interaction between drug and severity of pre-treatment patients on drug response. Univariate analysis was used to examine the crude association between patients with hemorrhoids after treatment and independent factors. Two variables were significant (i.e. defecation behavior and severity of hemorrhoids). Logistic regression was used to determine the factors associated with an improvement in hemorrhoids after treatment. Variables in the model were considered together to explain variances in the dependent variables. In other words, together, the variables revealed an influence to explain dependent variance at the same time. The result from unconditional logistic regression was $R^2$,

with a value of 12.5%. The model could be used to explain the relationship between severity of hemorrhoids and the risk ratio of treatment at a moderate level. Four variables were significant in the logistic regression: type of work activity, defecation behavior, experience of hemorrhoids, and severity of hemorrhoids (grade of internal hemorrhoids). These are discussed as follows:

**Type of work activity**

The result showed that type of activity was not associated with hemorrhoids by univariate analysis. The work activities of the patients were heavy lifting and standing daily (RR = 0.53, 034), respectively. This result was different from other studies because 72% of the patients worked regularly. This study found that type of work activity was not associated with hemorrhoids.

**Defecation behavior**

The result revealed that defecation behavior was significantly associated with hemorrhoids. About 58% of patients had constipation and constipation was associated with hemorrhoids (RR=1.36). Diarrhea was also associated with hemorrhoids (RR = 1.95). This was confirmed with the results of Stewart et al. (12), Johanson and Sonnenberg (13), Delco and Sonnenberg (14), and Chaiarelli P. et al. (22).

**Experience of hemorrhoids**

The result of this study showed that experience of hemorrhoids was not associated with hemorrhoids. This result was different from other studies because 72% of the patients worked regularly. This study found that type of work activity was not associated with hemorrhoids.

**Severity of hemorrhoids (grade of internal hemorrhoids)**

The result revealed that severity of hemorrhoids was significantly associated with improvement in hemorrhoids after treatment. This result supported by Sumboonnanonda K. and Lertsithichai P. (24), and Chaleoykitti B. (25).

These variables were significant in logistic regression but only severity of hemorrhoids (grade of internal hemorrhoids) was in the selected model, because severity of hemorrhoids and interaction between treatment and severity of the pre-treatment patient could well explain response to treatment in the logistic regression model. The three variables remaining were nuisance parameters, and therefore these variables were not considered in the model.

# CHAPTER VI
# CONCLUSION AND RECOMMENDATIONS

## 6.1 Conclusion

The relationships between the selected variables and improvements in the severity of hemorrhoids patients in Rajavithi, Chonburi, and Sriracha hospitals were tested by logistic regression analysis. Although statistical testing did not show significant coefficients of treatment by logistic regression, it gave an explanation for the interaction effect of treatment. It was found that Pet-sang-kart in the severe group yielded the highest risk ratio, at 1.46. These patients were severe hemorrhoid cases who had received Pet- sang-kart, and would have 1.46 times greater improvement in severe hemorrhoids than those who had received the placebo. Meanwhile, other risk ratio values were close to one (RR = 1.07 and 0.95) for Pet-sang-kart and Daflon in moderate hemorrhoids patients, respectively. This revealed that moderate hemorrhoids patients who received Pet-sang-kart would have a risk ratio of 1.07 times, or for Daflon 0.95 times, so that these treatments did not improve moderate hemorrhoids differently from the placebo. Pet-sang-kart was better for treating severe hemorrhoids patients.

## 6.2 Recommendations

### 6.2.1 Recommendations for clinical effects

1. The effects of treatment for curing hemorrhoids were not obvious. Due to the sample size in this study, there were excessive numbers of patients with mild hemorrhoids (Grade I). However, a large sample size should be studied, and patients with severe hemorrhoids should be included in clinical trials.

2. Most patients did not have severe hemorrhoidal symptoms. Hemorrhoidal symptoms had four levels, and these levels should decreased by two levels for treatment effects to be apparent.

3. The pathogenesis of hemorrhoids should be cured in non-severe cases who treat themselves. So, the treatment effect is not obvious.

### 6.2.2 Recommendations for future study

The conditional logistic regression model can be used to explain the relationships between treatment and the probability of disease improvement. However, a large sample size should be studied to increase the category of variables. In particular, patients with severe hemorrhoids should be included in clinical trials, for a clearer and more unambiguous explanation. Highly severe hemorrhoids patients were not included in the study.

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# APPENDIX

# APPENDIX
# STATICAL ANALYSIS

## 1. Chi – square Test

The chi-square distribution is used to test hypotheses, where the data available for analysis are in the form of frequencies. These hypotheses testing procedure is tests of independent.

| Factor B | Factor A | | Total |
|---|---|---|---|
| | 1 | 2 | |
| 1 | $O_{11}$ | $O_{12}$ | $R_1$ |
| 2 | $O_{21}$ | $O_{22}$ | $R_2$ |
| . | . | . | . |
| I | $O_{i1}$ | $O_{i2}$ | $O_i$ |
| Total | $C_1$ | $C_2$ | N |

$\chi 2 = \sum_i \sum_j (O_{ij}-E_{ij})^2 / E_{ij}$ ;i=1,j = 1,2

df = (r-1)

$O_{ij}$ = is the frequency, or number of counts, observed in class I

$E_{ij}$ = is the frequency expected in class I if the null hypothesis is true.

= $R_i C_j / N$

df = degree of freedom

Assumption of Chi - square (44)

1. The $\chi^2$ test is a large sample approximation ($n \geq 30$).
2. The expected frequency is a least 1 and should not be less than 5 over 20 percent
3. If the assumption (2) fail, neighboring classes should be collapse.

4. Only 2x2 table which violate assumption can be apply by Fisher exact's test.

**Logistic regression analysis**

**2.1 The logistic model** (40)

The model produced by logistic regression is nonlinear and important reference of the regression analysis concerns the nature of the relationship the outcome and more the one independent variable. Then the logit of the multiple logistic regression model is given by the equation

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \beta_p X_p$$

Logistic regression emphasizes the probability of a particular outcome for each case.

$$P(Yj = 1) = e^{(\beta 0 + \beta 1\, X1)} / [1+e^{(\beta 0 + \beta 1\, X1)}]$$
$$1 - P(Yj = 1) = 1 / [1+e^{(\beta 0 + \beta 1\, X1)}]$$

P = Probability of success on an event in subjects (Y = 1)

1-P = Probability of non – success on an event in subjects (Y = 0)

$$P/(1 - P) = \text{Odds}$$
$$P/(1 - P) = e^{(\beta 0 + \beta 1\, X1)}$$

The transformation is chosen so that the response function is made to be linear, as follows:

$$\text{Ln}\ [\frac{P}{1-P}] = \beta_0 + \beta_1 X_1$$

If $X_i$ for p predictors (i = 1,2,3,…,p) the logistic model equation creates the logit or log of the odds:

$$\text{Ln}\ [\frac{P}{1-P}] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \beta_p X_p$$

$X_i$ = independent variables; i = 1,2,3,…,p

$\beta_i$ = coefficient of variable $X_i$ ; i = 1,2,3,…,p

**Assumptions of logistic regression** (41, 42)

Assumptions of Logistic Regression are as follow:

1. The dependent variable is In odds which is transformed from an equation of $P = EXP(\alpha + \beta_i x_i) / 1 + EXP(\alpha + \beta_i x_i)$.
2. The independent variables are at least dichotomous scales or nominal scales.
3. Each variable in explanatory variable is independent from each other.
4. $\varepsilon_i$ is a normally distributed, with mean zero; $E(\varepsilon_i) = 0$ for all, $i = 1,2,3,\ldots,n$.
5. The variance of each $\varepsilon_i$ is the same; $Var(\varepsilon_i) = \sigma^2$.
6. $\varepsilon_i$ and $\varepsilon_j$ uncorrected, $i \neq j$, so that $cov(\varepsilon_i , \varepsilon_j) = 0$.

## 2.2 Estimation of logistic parameters (40)

Usually the basic function form can be written as

$$\pi(x_i) = [EXP(\sum_{j=0}^{k} \beta_j X_{ij})] / [1 + EXP(\sum_{j=0}^{k} \beta_j X_{ij})] \; ; \; i = 1,2,3,\ldots,k$$

The logistic model has been presented thus for without indicating how one estimates the parameter ($\beta_i$) from a set of data. In fact, the method of approaches is maximum likelihood estimation.

When more than one observation on Y occurs at a fixed $X_i$ value, it is sufficient to record the number of observations $n_i$ and the number of "1" outcomes.

Thus, let $Y_i$ refer to this "success" count rather than to the individual binary responses. The $\{Y_i , i = 1,2,3,\ldots,I\}$ are independent binomial random variable with

$E(Y_i) = n_i \pi(x_i)$, when $n_1 + n_2 + n_3 + \ldots + n_j = N$.

The joint probability mass function of $(Y_1,\ldots, Y_i)$ is probability to the product of I binomial function,

$$\begin{aligned} L &= \{\Pi^I_{i=1} \pi(x_i)^{yi} [1-\pi(x_i)]^{ni-yi} \\ &= \{\Pi^I_{i=1} [1-\pi(x_i)^{ni}]\} \{\Pi^I_{i=1} \exp[\log (\pi(x_i)/1-\pi(x_i)^{yi}]\} \\ &= \{\Pi^I_{i=1} [1-\pi(x_i)]^{ni}\} \exp [\Sigma\, y_i \log (\pi(x_i)/1-\pi(x_i))] \end{aligned}$$

The $i^{th}$ logit is $\Sigma_j \beta_j x_{ij}$, so the exponential term in the last expression equals $\exp[\Sigma_i y_i (\Sigma_j \beta_j x_{ij})] = \exp[\Sigma_j (\Sigma_i y_i x_{ij}) \beta_j]$. Also, since $[1-\pi(x_i)] = [1+ \exp(\Sigma_j \beta_j x_{ij})]^{-1}$,

The log likelihood equals

$$L(\beta) = \Sigma_j (\Sigma_i y_i x_{ij}) \beta_j - \Sigma_i n_i \log [1+\exp(\Sigma_j \beta_j x_{ij})]$$

When likelihood equation were derived by differentiation L with respect to element s of β and setting the results equal to zero. Since

$$\partial L / \partial \beta_a = \Sigma_i y_i x_{ia} - \Sigma_i n_i x_{ia} [\exp([\Sigma_j \beta_j x_{ij}] / 1+\exp(\Sigma_j \beta_j x_{ij})]$$
$$= 0 \quad ; a = 0,1,2,\ldots,p$$

However, the likelihood equations are nonlinear functions of the maximum likelihood estimates ( $\hat{\beta}_i$ ), and it requires iterative solution. Thus, the Newton-Raphson method is a method for solving nonlinear equation. It can solve likelihood equations, that determine the location at which is maximized.

In more detail, here is how the Newton- Raphson method determine the value ( $\hat{\beta}$ ) at which a function L(β) is maximized. Let $u' = \partial L(\beta) / \partial \beta_1 , \partial L(\beta) / \partial \beta_{2,\ldots})$, and let H denote the matrix having entries $h_{ab} = \partial^2 L(\beta) / \partial \beta_a \partial \beta_b$, called the *Hessian matrix*. Let $u^{(t)}$ , $H^{(t)}$ be u and H evaluated at $\beta^{(t)}$, the guess t for $\hat{\beta}$ . Step t in the iterative process (t = 0,1,2,…) approximated L(β) near $\beta^{(t)}$ by the terms up to second order in its Taylor series expansion.

Solving

$$\partial L(\beta) / \partial \beta \approx u^{(t)} + H^{(t)} (\beta - \beta^{(t)}) = 0$$

for β yields the next guess. That guess can be expressed as

$$\beta^{(t+1)} = \beta^{(t)} - (H^{(t)}) u^{(t)},$$
$$\beta^{(t+1)} = \beta^{(t)} + \{X' \text{ Diag } [n_i \pi_i^{(t)} (1-\pi_i^{(t)}) X]\}^{-1} X' (y - m^{(t)})$$

where $m_i^{(t)} = n_i \pi_i^{(t)}$

After making an initial guess $\beta^0$, the method requires an initial guess for the value that maximizes the function. When the function is suitable and / or the initial

guess is good. The end of iteration process would be occurred either by consideration on limitation of largest or convergence of $\beta^{(t)}$ become stable.

**2.3 Testing for the significance of the coefficients** (41)

The likelihood ratio for logistic regression plays the same role as the residual sum of squares plays in linear regression. The comparison of observed to predicted values using the likelihood function is based on the following expression

LR = -2 ln [(likelihood of the current model)/(likelihood of the saturated model)]

The quantity inside the large brackets in the expression above is called the likelihood ratio. Using minus twice its log is mathematical and is necessary to obtain a quantity whose distribution is known and thus can be used for hypothesis testing purposes.

For purpose of assessing the significance of an independent variable comparing the maximum likelihood estimate of the slope parameter, $\hat{\beta}_1$, to an estimate of its standard error. The resulting ratios, under the hypotheses that $\beta_1 = 0$, will follow a standard normal distribution.

$$\text{Wald} = \hat{\beta}_1 / \hat{\text{SE}}(\hat{\beta}_1)$$

**2.4 Model building process** (41)

There are certain steps one can follow to aid in the selection of variables for logistic regression model.

1. The criteria for inclusion of a variable in model base on the background of literature review on the factor association with LRI.

2. The selection process should begin with careful simple analysis of each variable. For the k level of the independent variable, the likelihood ratio chi-square with k-1 degree of freedom is exactly equal to the value of the likelihood ratio test for the significance of coefficients for the k-1 design variables in a univariate logistic regression model that contains that single independent variable.

3. Upon completion of the simple analyses we select variables for the multivariate analysis. Any variable whose univariate test has a p-value < 0.2 should be considered as a candidate for the multivariate model along with all variables of known biologic importance. Once the variables have been identified, we begin with a model containing all of the selected variables.

4. Following the fit of the multivariate model, the importance of each variable included in the model should be verified. This should include (a) An examination of Wald statistic for each variable and (b) A comparison of each estimated coefficient with the coefficient from the univariate model containing only that variable. Variables that do not contribute to the model based on these criteria should be eliminated and a new model fit. The new model should be compared to the old model through the likelihood ratio test. Also, the estimated coefficients for the remaining variables should be compared to those from the full model. In particular we should be concerned about variables whose coefficients have changed markedly in magnitude. This would indicate that one or more of the excluded variables were important in the sense of providing a needed adjustment of effect of variable that remained in the model. This process of deleting refitting and verifying continues until it appears that all of the important variables are included in the model and those excluded are either biologically or statistically unimportant.

5. Once we have obtained a model that contains the essential variables, we should look closely at the variables in the model and consider the need for including interaction terms among the variable.

**2.5 Goodness of fit** (41)

Goodness of fit is formally evaluated using the Hosmer-lemeshow statistic. A goodness of fit test is used that compare observed with expected frequencies in cells formed which proposed grouping base on the values of estimated probabilities. However, these statistics assume adequate expected dell frequencies between pairs of discrete predictors. Thus, deciles-of-risk statistics evaluate goodness of fit by creating ordered groups of subjects and then comparing the number actually in each group with the number predicted into each group by the logistic regression model.

Subjects are first put in order by their estimated probability on the outcome variables. Then subjects are divided into 10 groups according to their estimated probability with degree of freedom equal to 8 (k-p-1 = 10-1-1 = 8)

| Group | Expected | | Total | Observe | | Total |
|---|---|---|---|---|---|---|
| Range of risk | Y = 0 | Y = 1 | | Y = 0 | Y = 1 | |
| 1 (0.0 – 0.1) | $e_{01}$ | $e_{11}$ | $m_1$ | $O_{01}$ | $O_{11}$ | $m_1$ |
| 2 (0.1 – 0.2) | $e_{02}$ | $e_{11}$ | $m_2$ | $O_{02}$ | $O_{12}$ | $m_2$ |
| . | . | . | . | . | . | . |
| . | . | . | . | . | . | . |
| . | . | . | . | . | . | . |
| 10 (0.9 – 1.0) | $e_{0,10}$ | $e_{0,10}$ | $m_{10}$ | $O_{0,10}$ | $O_{0,10}$ | $m_{10}$ |
| | $n_0$ | $n_1$ | n | $n_0$ | $n_1$ | n |

$H_0$ = A good fit of model

$O_{11}$ = $\Sigma_i y_I$ = Total number of subjects with y = 1

$O_{11}$ = $\Sigma_i (1- y_i)$ = Total number of subjects with y = 0

$e_{11}$ = $\Sigma_i p(x_i)$ = The estimated expected value by summing the estimated probabilities over all subjects in a group with y = 1

$e_{01}$ = $\Sigma_i [(1- p(x_i))]$ = The estimated expected value by summing the estimated probabilities over all subjects in a group with y = 0

Hosmer-Lemeshow H* statistic = H* (29)

$$H^* = \sum_{k=0}^{1} \sum_{1=1}^{10} \left(O_{k1} - e_{k1}\right)^2 / e_{k1}$$

$$H^* = (O_{01} - e_{01})^2/ e_{01} + (O_{11} - e_{11})^2/ e_{11} + \ldots + (O_{1,10} - e_{1,10})^2/ e_{1,10}$$

$H^* = \chi^2$ with 8 d.f.

### 2.6 Pseudo $R^2$

$R^2$ is the proportion of variance of $x_1$ explained by the regression relationship with $x_1,\ldots,x_p$ which the ratio of the regression sum of squares to the total sum of squares. Let $L_0$ and $L_p$ denote the log-likelihoods for models containing only the intercept, and the model containing the intercept plus the p covariates, respectively. Hence, in linear regression

$$\text{Pseudo } R^2 = 100\,(L_0 - L_p) / L_0$$

### 2.7 Adjusted odds ratio

Rick factors were divided in 2 categories more, one group representing a reference category.

$$\text{Odds Ratio} = \exp(\hat{\beta}_i)$$

95% confidence interval of adjusted odds ratio.

An approximate $(1-\alpha)$ confidence interval for odds ratio $\psi$ (x* : x) is given by

$$= \exp[\Sigma\ \hat{\beta}_i (x_i^* - x_i)]$$

$$95\%\text{ CI for } \psi = \exp\{[\hat{\beta}_i (x_i^* - x_i)] \pm [Z_{\alpha/2} \sqrt{\sigma_{ii} (x_i^* - x_i)^2}\ ]\}$$

# BIOGRAPHY

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