# Frequency And Presentation Of Peptic Ulcer In Patients With Liver Cirrhosis Versus Non Cirrhotic Patients

*Thesis*

*Submitted for Fulfillment of*
*Master Degree in Tropical Medicine*


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# Acknowledgement

*First and foremost, thanks are due to "Almighty Allah", the beneficent , the merciful.*

*I would like to express my sincere gratitude gratefulness to Prof. Dr.Wahid Abd - ELmonsef professor of Tropical medicine, Faculty of Medicine, Ain Shams University who supervised this thesis and provided invaluable help during its execution.*

*I am also grateful and indebted to Dr. Amal Tohamey, Lecturer of Tropical medicine, Faculty of Medicine, Ain Shams University, for her guidance and supervision.*

*I am most thankful to my family since without , their encouragement and support, I would have not been able to accomplish this work.*

*Esmail Osman Esmail*

*Thanks to* ***ALLAH*** *for every thing I have. I would like to express my ever lasting gratitude to professor.* ***Dr. Amin Gad El-Rab Atta,*** *Professor of Ophthalmology, Faculty of Medicine Ain Shams University, for his kindness, generosity and supervision for me in this work.*

*My sincere and great appreciation to* ***Dr. Sherein Shafik Wahba,*** *Lecturer of Ophthalmology, Faculty of Medicine, Ain Shams University, for her continuous support, encouragement and valuable instructions .*

*I wish to express my deep gratitude and thanks to all my dear professors and colleagues.*

*I dedicate this work to my family and my friends.*

***Mohamed Radwan***

*Thanks to ALLAH for every thing I have. I would like to express my ever lasting gratitude to professor. **Dr. Amin Gad El-Rab Atta,** Professor of Ophthalmology, Faculty of Medicine Ain Shams University, for his kindness, generosity and supervision for me in this work.*

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**Mohamed Radwan**

# Introduction

Peptic ulcer disease (PUD) continues to have a significant impact on society, with a cumulative lifetime prevalence of ٨٪ to ١٤٪ ***(Delvalle et al., ٢٠٠٣)***.

Peptic ulcer disease (PUD) is common and frequently is diagnosed in patients with well known dyspeptic symptoms after confirmation by endoscopy or barium contrast radiography. The pathogenesis of the symptomatology of PUD is largely unknown. A few studies have suggested that several factors, such as acid, inflammation, or muscle spasm, may be involved in the pathogenesis of ulcer pain ***(McColl and Fullarton, ١٩٩٣)***.

Pain sensitivity has been shown to decrease with age in animal and human studies. This includes both cutaneous and visceral pain ***(Crisp and Smith, ١٩٩٨)***. This reduction may help explain reports of atypical or late clinical presentation of illness in the elderly ***(Coleman and Denham, ١٩٨٠)***.

Traditionally, the main pointer to the presence of peptic ulcer is abdominal pain or discomfort usually but not always located in the epigastrium. In the event of pain not being present, the diagnosis is missed or only occurs on the development of complications ***(Sturdevant and Walsh, ١٩٧٨)***.

Some patients with PUD are asymptomatic until life-threatening complications (e.g., hemorrhage, perforation) develop. The prevalence of ulcers that do not cause symptoms among the general population is unclear ***(Corinaldesi et al., ١٩٩١).***

Many studies show that there is an increased frequency of peptic ulcer in patient with cirrhosis ***(Rabinovitz et al., ١٩٩٠)***.

The prevalence of peptic ulcer in cirrhotic patients, reaching a point prevalence of ١١,٧٪. Compared with the general population, patients with cirrhosis have higher bleeding complications, delayed healing, and greater ulcer recurrence rates ***(Sebastino et al., ١٩٩٥).***

In cirrhosis little information is available about the clinical features of the ulcers, the response to therapy, the risk of complications, and the need for endoscopic follow up ***(Sebastino et al., ١٩٩٥)***.

***Sebastino et al., (١٩٩٥)*** said that peptic ulcer was not only more frequent in cirrhosis but usually occurred without concomitant abdominal pain and was often complicated by bleeding.

# Aim of the work

To assess the frequency of peptic ulcer in cirrhotic patients compared with non cirrhotic patients.

To evaluate the mode of presentation of peptic ulcer in cirrhotic patients compared with non cirrhotic patients.

## ١ -Introduction

Peptic Ulcer Disease (PUD), non-malignant duodenal and gastric ulcers, is an important disease entity, responsible for considerable morbidity and mortality. Our understanding of the etiology , pathogenesis and approach to treatment have undergone remarkable changes in the last ٣٠ years. Up to the early ١٩٨٠s, PUD was seen as a disease of excessive gastric acid production and its treatment ranging from medical to surgical approach . The recognition that PUD was associated with Helicobacter pylori infection causes some change in the approach to this disease. Concurrently, very powerful drugs to lower gastric acid secretion and heal ulcers have been developed. (**Yuan et al.,** ٢٠٠٦).

## ٢-Definition of PUD

Peptic ulcer disease (PUD) is a group of disorders involving the upper gastrointestinal (GI) tract. peptic ulcer is defined as abraded area of the GI mucosa, typically located in the stomach or the first few centimeters of the duodenum ( **Guyton,** ١٩٩١).

## ٣- Epidemiology and history of PUD

The epidemiology of PUD disease changed dramatically in Europe and North America during the ٢٠th century. The early twentieth century showed a rapid rise in the incidence of duodenal ulceration in westernized societies.( **Hawkey,٢٠٠٠)**. Deaths from PUD had risen

discordantly in both sexes in the latter part of the ١٩th century. In ١٩٠٠, duodenal ulcer became extremely common, affecting up to ١٠٪ of males. Then in the ١٩٥٠s incidence and mortality rates began to fall. In a landmark paper in ١٩٦٢ Susser and Stein ( **Susser and Stein ,١٩٦٢**) interpreted this data . In ١٩٦٢, experts suggested that an environmental factor found in the late ١٩th century and early ٢٠th century in the western world caused a cohort effect on individuals born at such time. Environmental factors associated with early urbanization, social stress and with the economic crisis after world war were incorrectly regarded as predisposing factors to the disease **(Susser and Stein ,١٩٦٢)**.

It was only ٢٠ years later that the discovery by Marshall and Warren (***Marshall and Warren,*** ) of an unidentified bacilli in the stomach of PUD patients ushered in the new era. Since that time this bacterium, Helicobacter pylori, has not only been established as the major cause of PUD, but also, as humanity's most ubiquitous chronic bacterial pathogen, it evidences extremely complex ethno-geographic variations in epidemiology and pathogenicity. In the developed world, mortality from PUD has generally continued to decline (data from Asia show a lag, perhaps reflecting delayed development (**Lame et al., ٢٠٠٠**) in association with falling infection rates as well as better diagnostic and therapeutic efforts. (**Baron and Sonnenberg, ٢٠٠٢**).

Recently the incidence of PUD in general population is estimated by American gastroenterological association which reported that there are ٣٥٠،٠٠٠ to ٥٠٠،٠٠٠ new cases of peptic ulcer per year. (**American Gastroenterological Association , ٢٠٠٧ ).**While the prevalence of PUD in cirrhosis is reported from endoscopy screening studies, is aproximately

٥—٢٠٪ when compared with ٢—٤٪ of the general population (**Tsai,١٩٩٨**).

**Epidimiological and historical aspects of PUD:-**

**١ - Occurrence of ulcer disease:**

It seems probable that most of the older surveys, based on symptomatic or radiologic diagnosis , can not properly be evaluted in terms of real ulcer frequency since the endoscopic examination detects up to twice as many ulcers as the ordinary barium meal study. There have apparently been tremendous changes in the incidence of ulcer during the past two centuries. During the ١٩th Century, ulcers were usually gastric that occurred in young women, often under ٢٠ years old and of low social class. On the other hand, these ulcers were very rare in pregnancy **(Hunt and Milton , ١٩٨٠)** . Mortality and hospital admission rates for peptic ulcer in England and Wales have fallen over the last ٢٠ years **(Barker et al,** ١٩٨١) . These changes started before the discovery of the new and effective forms of medical treatment for peptic ulcer. However, **(Wyllie et al, l٩٨١)** said that the observed fall in the number of peptic ulcer surgical procedures reflects clinical fashion, rather than a decrease in the prevalence of active ulcer diseases.

**٢ -Age Occurrence:**

Western Europe has experienced a progressive increase in the peak age of occurrence of ulcers since the beginning of the century. In less developed countries, the peak prevalence and incidence rates occur in younger age groups **(Moshal et al, ١٩٨١).**

**٣ - Sex Distribution:**

One of the most striking features of the epidemiology of peptic ulcer has been the dramatic change in its sex distribution during the past century. There was a marked female preponderance of about ٥ : ١ in the ١٩th century. The ratio became equal in about ١٩١٥, after which male preponderance started **(Langman, ١٩٧٣).** In the ١٩٥٠s, when the frequency of peptic ulcer seemed to attain a peak in most western countries, both gastric and duodenal ulcers were more common in men than in women. The frequency of peptic ulceration was estimated as ٨,٣ % for men and ٣,٩٪ for women **(Sleisenger, ١٩٧٣).**

**٤ - Seasonal occurrence:**

It is a widely held view, with presumed etiologic implications, that there is an increased frequency of new ulcers and recurrences during certain seasons,especially during autumn and winter months. However, the matter is controversial, and it has also been stated that in different parts of the world, and even in the same geographic areas, there is a peak in every month except July **Gibiniski et al, in (١٩٨٢)** found that there was a maximal ulcer frequency in February and September, with values significantly higher than in August and December. They concluded that, the seasonal increase in ulcer fre quency,if there is one, may be related to the occurrence of upper respiratory tract infections or to the treatment of such infections (e.g. with aspirin) . Alternatively it has been reported that experimental ulcers in animals show a significantly decreased frequency during the summer, so that summer—related ‘ protective’ factors may also be involved.

## ٤- Aetiology and predisposing factors of PUD

**- Helicobacter – pylori infection**

H. pylori produces disease through a variety of processes In the stomach, the bacteria colonizes the gastric mucosa by adhering to the cell surface (through expression of Lewis blood group antigens and lipopolysaccharide [LPS], producing urease, cagA gene products, and antibacterial peptides (cecropins). H. pylori avoids host defenses by shedding bacterial proteins, by detoxifying reactive oxygen free radicals, and through the innately low biologic activity of H. pylori LPS. H. pylori can directly injure the host through the production of urease and the release of various hemolysins, cytotoxins (vac A) and LPS. Damage also occurs through the immune system as the host mounts an immune response with increased cytokine production and the subsequent migration and activation of mononuclear cells and phagocytes (**Brian and Justin,٢٠٠١**) .

**- Non steriodal Anti-inflammatory Drugs (NSAIDS) and Aspirin**

It has long been recognized that aspirin and other non-steroidal anti-inflammatory agents. which inhibit prostaglandin formation, can cause peptic ulcer disease,particularly gastric ulcers (**Wallace,٢٠٠٥**). The extremely widespread use of these agents in the West, for a variety of medical conditions, has increased the significance of these complications. H. pylori infection and NSAID use are independent and synergistic risk factors for uncomplicated and bleeding peptic ulcer (**Papatheodoridis et al.,٢٠٠٦).** The substitution of these agents by COX-٢ inhibitors has not had much influence on peptic ulcer complications.Prostaglandins (misoprostol), proton pump inhibitors and double dose histamine ٢ receptor antagonists (H٢RAs) are effective in

preventing NSAID related PUD (**Yeomans,٢٠٠٢**). The importance of NSAIDs as a cause of peptic ulceration has increased, and low-dose aspirin is now the fastest growing cause of ulcer complications **(Pirmohamed et al ., ٢٠٠٤ ).**

**-Neither H. pylori nor NSAID**

The percentage of non-H.pylori and non-NSAID PUD is also increasing at least in the West (**Quan and Talley,٢٠٠٢**). Inability to detect actual H. pylori infection needs to be assessed carefully.Recent or current use of antibiotics, PPIs or bismuth agents may cause errors. In non-H.pylori, non-NSAID ulcers the Zollinger-Ellison syndrome needs to be excluded. Other infections such as CMV may be important in HIV positive patients. Crohn's disease may give rise to gastroduodenal ulceration which mimics PUD (**Howden and Leontiadis,٢٠٠١**).

| CAUSES AND RISK FACTORS | |
|---|---|
| COMMON AND UNCOMMON CAUSES OF PEPTIC ULCERATION | |
| **Causes of peptic ulcer** | **Main mechanisms** |
| **COMMON** | |
| *Helicobacter pylori* | Inflammation, toxin, acid |
| NSAIDs | Compromised mucosal defence |
| **LESS COMMON** | |
| Zollinger-Ellison syndrome<br>Multiple endocrine neoplasia<br>Systemic mastocytosis | Acid hypersecretion |
| Duodenal Crohn's disease | Inflammation |
| Radiation<br>Stress ulcers<br>Celiac axis stenosis<br>Hepatic artery chemotherapy | Ischemia or compromised mucosal defence |
| **CONTROVERSIAL** | |
| Corticosteroids | Enhance risks in NSAID users |
| Idiopathic | Some cases represent missed *H. pylori* or NSAIDs |

- **Table (١)** based on data from (**Quan and Talley,٢٠٠٢**)

**-Controversies**

There is continuing debate about whether corticosteroids alone can cause ulcers," although the ability of corticosteroids to enhance NSAID-associated ulcers is well established . (**Chan and Leung,٢٠٠٢**). Idiopathic ulcers are rare. Most are probably due to falsely negative H. pylori tests or sporadic or surreptitious NSAID use. If these causes are confidently excluded, rare conditions such as those described above should be sought. However, a small group of idiopathic peptic ulcers still exist and, because of falling H. pylori prevalence, the proportion of peptic ulcers that are idiopathic is likely to be increasing. (**Quan and Talley,٢٠٠٢).**

**Other factors associated with peptic ulcer disease:**

**- Smoking and Peptic Ulcer Disease:**

Peptic ulcer is a common disorder of gastrointestinal system and its pathogenesis is multifactorial, where smoking and nicotine have or significant adverse effects. Smoking stimulate basal acid output which is more pronounced in the smokers having duodenal ulcer. This increased gastric acid secretion is mediated through stimulation of H٢ receptor by histamine released after mast cell degranulation and due to the increase of the functional parietal cell volume or secretory capacity in smokers. Smoking and nicotine stimulate pepsinoge secretion and increase chief cell number with an enhancement of their secretory capacity. Long-term nicotine administration rate also significantly decreases total mucus neck cell population and neck-cell mucus volume. Smoking also increases bile salt reflux rate and gastric bile salt concentration increasing duodenogastric reflux that raises the risk of gastric ulcer in smokers. Smoking and nicotine not only induce ulceration, but they also potentiate ulceration caused by H. pylori, alcohol and nonsteroidal anti-

inflammatory drugs. Polymorphonuclear neutrophils (PMN) play an important role in ulcerogenesis through oxidative damage of the mucosa by increasing the generation of reactive oxygen intermediates (ROl), which is potentiated by nicotine and smoking. Nicotine by a cAMP-protein kinase system elevates the endogenous vasopressin level, which plays an aggressive role in the development of gastroduodenal lesions. Smoking increases production of platelet activating factor (PAF) and endothelin, which are potent gastric Ulcerogens. Cigarette smoking and nicotine reduce the level of circulating epidermal growth factor (EGF) and decrease the secretion of EGF from the salivary gland, which are necessary for gastric mucosal cell renewal. Nicotine also decrease prostaglandin generation in the gastric mucosa of smokers, thereby making the mucosa susceptible to ulceration. Smoking or smoke extract impairs both spontaneous and drug-induced healing of ulcer. Smoke extract also inhibits gastric mucosal cell proliferation by reducing ornithine decarboxylase activity, which synthesizes growth- promoting polyamines. It is concluded that gastric mucosal integrity is maintained by an interplay of some aggressive and defensive factors controlling apoptotic cell death and cell proliferation and smoking potentiates ulcer by disturbing this balance (**Maity et al.,٢٠٠٣**).

**Role of Psychological Factors:**

The role of psychological factors in the pathogenesis and natural history of PUD has been the subject of numerous studies, with conflicting conclusions. Early studies described certain personality characteristics thought to be markers for ulcer risk, including conflicts about dependency needs, hypochondriasis, and low ego strength. However, studies of patients in whom the diagnosis of duodenal ulcer disease was established endoscopically and with adequate controls concluded that