

# Gender and Time Trend of Liver Cirrhosis Mortality and Its Estimated Avoidable Proportion in a Mountainous Province of Viet Nam from 2005 To 2018

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**Keywords:** Liver Cirrhosis; Mortality Trend; Premature Death; Viet Nam

**Abbreviations:** CDC: Center for Diseases Control; CHS: Commune Health Stations ; ASR: Age-Standardized Rates

## ABSTRACT

**Objectives:** The aim was to estimate mortality rates, time trends by sex, and its estimated avoidable proportion of death due to cirrhosis in Lang son Province from 2005 to 2018.

**Methods:** We accessed a database of population-based mortality registration conducted yearly in 226 state health centers of 11 cities/districts of the Lang Son province to derive 2,612 death cases during 2005-2018. The variables of each case included the patient ID, age, sex, date, the cause of death, ICD-10 code. Mortality rates ratio and 95% confidence interval (MRR, 95%CI), age-standardized mortality rates (ASR), and an avoidable proportion of death were estimated.

**Results:** There was 88.5% of total premature deaths occurred under the age of 70. The estimated ASR per 100,000 was remarkably higher in men (63.2) than women (7.3). When compared to women, the estimated avoidable proportion was 88.5% of 2,321 death cases in men. The estimated mortality rates ratios, the year 2018 versus 2005, were significantly increased in men, MRR (95%CI): 1.367 (1.104, 1.693), p=0.004; but significantly decreased in women, MRR (95%CI): 0.344 (0.177, 0.668), p=0.002.

**Conclusion:** The findings suggested that Liver Cirrhosis is a preventable disease and primary prevention and screening for the disease at an early stage would be highly needed to reduce premature deaths occurred in communities.

## Introduction

During 1980-2017, Liver Cirrhosis was the major mortality of liver diseases worldwide [1]. The disease is chronic progressive liver fibrosis due to lifestyles and environmental factors [2]. In the initial stages, patients who suffered from liver cirrhosis are asymptomatic and the disease incidence rates are commonly underestimated [3]. Once clinical symptoms occur, the morbidity and premature death

resulting from cirrhosis increase sharply [4]. Liver diseases due to chronic infection with hepatitis viruses [5-8] and high consumption of alcohol [9] have been observed to be common in Viet Nam from the last century to date. Harmful usage of alcohol, chronic infection with hepatitis viral infection, and smoking might be responsible for cirrhosis. Previous results have pointed out the major risk of

cirrhosis was "Alcoholism" in many countries [10-13]. Based on these facts and figures, we have hypothesized that liver cirrhosis is a lifestyle-related health event and a possible avoidable disease. Patients suffering from liver cirrhosis need frequent medical care and their quality of life is affected [14]. Patients with liver cirrhosis have significantly increased morbidity and mortality [15]. However, few studies have been performed to address this public health problem in Viet Nam to date. This study aimed to estimate mortality rates, time trends by sex, and to estimate an avoidable proportion of death due to cirrhosis in men in Lang son Province from 2005 to 2018.

## Methods

The study was performed in Lang Son province, a mountain highland province in northern Viet Nam. The study population is bordering Guangxi province in China and other provinces in Viet Nam. It was a population-based mortality registration operated by the Lang Son Center for Diseases Control (CDC) that covered all 226 communes of 11 cities/districts of the province, with a population of 790,500 people in 2018 [16]. In Viet Nam, the national mortality registration systems have been started from 1992 that was following the guideline by the Ministry of Health to report the causes of death from all health facilities nationwide. From 1992 to date, Lang Son is one of all 63 cities/provinces of the country to actively conduct mortality registration based on the medical records available at 226 state commune health stations (CHS), 10 district general hospitals, 9 district out-patient clinics, and 3 provincial general and specialized hospitals. The head of the CHS is a person in charge of the monthly report of all death cases that occurred at his/her communes in a mortality registration book, named A6-mortality book that was designed by the Ministry of Health. The variables included name, age, sex, ethnicity, address, occupation, date, and cause of death, place of death occurred (at a health facility, home, other), and attended emergency care at the endpoint (Yes/no), and the name of the reporter.

From 2005 to date, the Lang Son CDC has collected data from all 226 CHS using the data collection form in the hard copy of "Mortality Registration" for six variables of name, age, sex, occupation, date, and cause of death for every year. The additional guidelines to determine the causes of deaths, including the immediate cause of death, a contributing cause of death, and the underlying cause of death, and its ICD-10 code, were sent with the designed form of "Mortality Registration". The average population number by sex has also been collected by this form for every year from 2005 to 2018. A yearly population structure by age groups of (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+) by sex was estimated using the results of the National Census conducted in 1999, 2009, and 2019.

The collected variables of each death case were inputted in Excel for each district for each year. The ID and ICD-10 code for the cause of death was made for each case. In this way, a database of mortality from 2005 to 2018, missing data for 2009-2010, was made by the Lang Son CDC. The dataset included 49,253 reported death cases due to all causes [16,17].

We accessed to Lang Son database of mortality during 2005-2018, missing data for 2009-2010, to derive variables of case's ID, age, sex, date, and cause of death, ICD-10 code. We found ICD-10 code K74 for Liver Cirrhosis and a total number of 2,612 cases for the present study. We also derived the average number of population by years and by communes for further estimate number of person-year for the final analysis. We calculated the mortality rates ratio with a 95% confidence interval (MRR, 95%CI) using regression analysis, adjusted for age groups of 10-year intervals (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+) and sex. Age-standardized rates (ASR) per 100,000 person-years were calculated using the world population structure as the standard. We calculated the avoidable proportion of deaths in men by the formulation of  $((a-b)*100/a)$  (a: ASR in men; b: ASR in women). The Board of Ethics in Bio-Medical Research at University of Medicine and Pharmacy at Ho Chi Minh City #106/UMP-BOARD, on 20 March 2019 and Hanoi Medical University Review Board in Bio-Medical Research # 61/HMURB, on 25 November 2008 have approved the present research protocol.

## Results

Overall, a total of 2,612 deaths were registered among residents in Lang Son Province from 2005 to 2018. Table 1 shows the results of deaths were 2,321 in men and 291 in women. Men had a higher age-adjusted mortality rate (ASR-WHO 63.2 per 100,000) due to cirrhosis compared to women (ASR-WHO 7.3 per 100,000), giving man to women ratio: 8.7/1 (63.2/7.3). The estimated men to women ratio were sharply increased from 4.9/1 (49.1/10.1) in 2005 to 18.6/1 (63.1/3.5) in 2018. Compared to women, the estimated avoidable proportion of death from Liver Cirrhosis in men was  $((63.2-7.3)*100)/63.2=88.5\%$ . There was 88.5% of total premature deaths occurred under the age of 70, Table 1. The age-standardized death rate increased gradually according to WHO-ASR from 27.7 per 100,000 to 33.4 per 100,000 person-years for both genders from 2005 to 2018, respectively. The estimated proportion of deaths due to Liver Cirrhosis was 5.3% (2,612 cases of Liver Cirrhosis vs. 49,253 total death cases) in both genders. Overall death due to the disease, men, and women combined, was significantly increased from 2005 to 2018. After adjusting for age and sex, per-year increment was significantly seen, MRR (95%CI): 1.019 (1.009, 1.028),  $p=0.001$  (Table 2).

**Table 1:** Mortality due to Liver Cirrhosis by sex during 2005-2018 in Lang Son province.

Sex	Year	Cause	Total	Crude rate &	ASR @	%<70 #	WHO \$
Men	2005-18	K74	2,321	51.4	57.8	91.3	63.2
Women	2005-18	K74	291	6.4	6.6	66.3	7.3
Men and women	2005-18	K74	2,612	28.8	30.3	88.5	33.1

Note: Missing data for the year 2009-2010; &: Crude rate per 100,000 person-years; \$: Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025; # Proportion of death cases aged under 70 year-olds. @: Age-standardized rate per 100,000 person-years using the SEGI World standard population (in the 1960s). Men to women ratio (ASR-WHO) = 8.7 (63.2/7.3). The estimated proportion of death from Liver Cirrhosis in men was  $\{(63.2-7.3)*100\}/63.2=88.5\%$

**Table 2:** Mortality due to Liver Cirrhosis in both genders by year from 2005 to 2018 in Lang Son province.

Year	Case	Crude rate &	%<70 #	WHO-ASR \$	MRR (95%CI) \$\$	p
2005	173	24.1	85.5	27.7	1.00 (reference)	
2006	163	22.3	85.3	26.0	0.926 (0.748, 1.147)	0.484
2007	190	25.9	84.2	29.5	1.075 (0.875, 1.320)	0.493
2008	188	25.2	92.6	29.4	1.049 (0.853, 1.289)	0.653
2011	235	32.1	83.4	37.0	1.333 (1.096, 1.623)	0.004
2012	225	30.1	86.2	34.2	1.253 (1.028, 1.528)	0.026
2013	243	33.0	89.7	37.9	1.370 (1.127, 1.665)	0.002
2014	269	34.5	90.3	39.8	1.432 (1.183, 1.734)	<0.001
2015	246	31.3	85.8	35.5	1.230 (1.070, 1.579)	0.008
2016	249	31.7	89.6	37.1	1.319 (1.087, 1.602)	0.005
2017	209	26.3	93.3	30.3	1.093 (0.894, 1.337)	0.387
2018	222	28.3	95.0	32.4	1.178 (0.965, 1.437)	0.107

Note: Missing data for the year 2009-2010; the estimated proportion of deaths due to Liver Cirrhosis was 5.30% (2,612 cases of Liver Cirrhosis vs. 49,253 total cases), both genders. \$\$ adjusted for age group (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+) and sex. Per-year increment MRR (95%CI): 1.019 (1.009, 1.028),  $p<0.001$ . & Crude rate per 100,000 person-years; \$ Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025; # Proportion of death cases aged under 70 year-olds. When combined all cases from 2005-2018, both genders, WHO-ASR: 31.3 per 100,000 person-years.

In men, the estimated proportion of deaths due to Liver Cirrhosis was 7.4% (2,321 cases of Liver Cirrhosis vs. 31,262 total cases). The age-standardized mortality rates per 100,000 were increased from 49.1 in 2005 to 65.1 in 2018. The estimated mortality rates ratios, the year 2018 versus 2005, were significantly increased, MRR (95%CI): 1.367 (1.104, 1.693),  $p=0.004$ . During this period, per-year increment was significantly observed, MRR (95%CI): 1.028 (1.018, 1.038),  $p=0.001$  (Table 3). In Women, the estimated proportion of deaths due to Liver Cirrhosis was lower (1.6%, 291 cases of Liver Cirrhosis vs. 17,990 total death cases)

than in men (7.4%, 2,321 cases of Liver Cirrhosis vs. 31,262 total death cases). For a time trend, in contrast, death due to the disease was significantly decreased in women from 2005 to 2018. The estimated mortality rates ratios, the year 2018 versus 2005, were significantly decreased, MRR (95%CI): 0.344 (0.177, 0.668),  $p=0.002$ . During this period, per-year decrement was significantly seen, MRR (95%CI): 0.948 (0.923, 0.974),  $p=0.001$  (Table 4). By age-specific, the estimated mortality rates per 100,000 in men were much higher than in women for all age groups, especially for the age group (50-59), 193.5 versus 13.2, respectively (Figure 1).

**Table 3:** Mortality due to Liver Cirrhosis in men by year from 2005 to 2018 in Lang Son province.

Year	Case	Crude rate &	%<70 #	WHO-ASR \$	MRR (95%CI) ##	p
2005	141	39.4	86.5	49.1	1.00 (reference)	
2006	138	37.9	87.0	47.6	0.962 (0.761, 1.217)	0.748
2007	166	45.4	88.6	55.3	1.152 (0.920, 1.442)	0.216
2008	156	42.7	95.5	51.3	1.068 (0.850, 1.341)	0.574
2011	201	55.1	88.6	69.0	1.400 (1.128, 1.736)	0.002
2012	200	53.9	89.0	65.4	1.367 (1.102, 1.697)	0.004

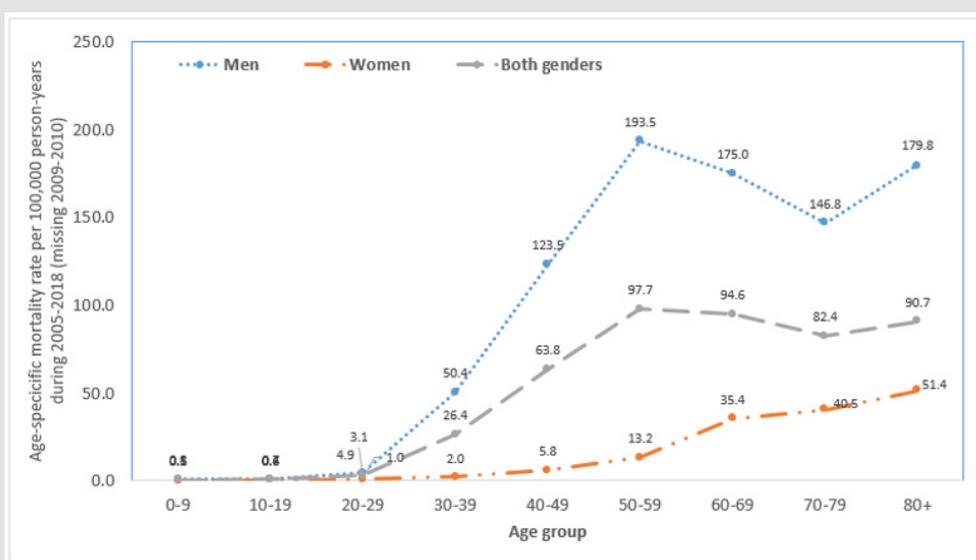
2013	221	60.2	92.3	73.5	1.530 (1.238, 1.890)	<0.001
2014	241	62.0	92.9	75.9	1.575 (1.279, 1.940)	<0.001
2015	216	55.2	88.4	67.3	1.401 (1.133, 1.732)	0.002
2016	234	59.9	91.5	75.8	1.522 (1.235, 1.876)	<0.001
2017	197	49.8	94.9	61.6	1.264 (1.019, 1.570)	0.033
2018	210	53.9	97.6	65.1	1.367 (1.104, 1.693)	0.004

**Note:** Missing data for the year 2009-2010; the estimated proportion of deaths due to Liver Cirrhosis was 7.42% (2,321cases of Liver Cirrhosis vs. 31,262 total cases) in men. ## adjusted for age group (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+). Per-year increment MRR (95%CI): 1.028 (1.018, 1.038), p<0.001. & Crude rate per 100,000 person-years; \$ Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025; # Proportion of death cases aged under 70 year-olds. When combined all cases from 2005-2018 in men, WHO-ASR: 63.2 per 100,000 person-years.

**Table 4:** Mortality due to Liver Cirrhosis in women by year from 2005 to 2018 in Lang Son province.

Year	Case	Crude rate &	%<70 #	WHO-ASR \$	MRR (95%CI) ##	p
2005	32	8.9	81.3	10.1	1.00 (reference)	
2006	25	6.8	76.0	7.9	0.768 (0.455, 1.296)	0.323
2007	24	6.5	54.2	7.3	0.734 (0.432, 1.246)	0.252
2008	32	8.5	78.1	10.2	0.965 (0.591, 1.575)	0.886
2011	34	9.2	52.9	9.8	1.043 (0.643, 1.690)	0.865
2012	25	6.7	64.0	7.8	0.753 (0.446, 1.270)	0.287
2013	22	5.9	63.6	7.0	0.671 (0.390, 1.154)	0.149
2014	28	7.1	67.9	8.4	0.806 (0.485, 1.338)	0.404
2015	30	7.6	66.7	8.3	0.857 (0.521, 1.410)	0.544
2016	15	3.8	60.0	4.2	0.430 (0.233, 0.793)	0.007
2017	12	3.0	66.7	3.5	0.339 (0.175, 0.659)	0.001
2018	12	3.0	50.0	3.5	0.344 (0.177, 0.668)	0.002

**Note:** Missing data for the year 2009-2010; the estimated proportion of deaths due to Liver Cirrhosis was 1.62% (291 cases of Liver Cirrhosis vs. 17,990 total cases) in women. ## adjusted for age group (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80+). Per-year increment MRR (95%CI): 0.948 (0.923, 0.974), p<0.001. & Crude rate per 100,000 person-years; \$ Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025; # Proportion of death cases aged under 70 year-olds. When combined all cases from 2005-2018 in women, WHO-ASR: 7.3 per 100,000 person-years.



**Figure 1:** Age-specific mortality rate per 100,000 person-years by sex during 2005-2018 due to Liver Cirrhosis.

**Note:** Missing data for the year 2009-2010;

## Discussion

We observed a divergence over time from 2005 to 2018 between men (statistically significant increase) and women (statistically significant decrease) in a community in the mountainous province of Lang Son in northern Viet Nam. When compared to women, the estimated avoidable proportion of death due to the disease was about 88.5% in men. There was serious premature death, as high as 88.5% for both genders (91.3% in men and 66.3% in women). The findings suggested that Liver Cirrhosis is a preventable disease and performing primary prevention in the community to reduce premature death would be highly needed. Harmful usage of alcohol by men living in the Lang Son province might be the major risk factor of developing Liver Cirrhosis. An estimated annual amount of pure alcohol consumption in 2010 was 12.1 liters and 0.2 liters in men and women, respectively [18]. This big gap between men and women can be consistent with the significantly higher risk of death from Liver Cirrhosis in men than in women. Between men and women, there were no significant differences for both Hepatitis B virus, HBsAg positive (Odds ratio and 95% confidence interval, men versus women: 0.76 (0.54–1.01)) and Hepatitis C virus infection (Odds ratio and 95% confidence interval, men versus women: 1.73 (0.41–7.28)) [5,19].

Therefore, viral Hepatitis infection could not be explained for the big gap between genders in the risk of death from this disease. The present findings support our hypothesis that liver cirrhosis is a lifestyle-related health event and a possible avoidable disease. The results warrant further observational studies to conclude the association between alcoholism and Liver Cirrhosis in the disadvantaged areas in Viet Nam with emphasis on primary prevention of the disease. There was rarely alcohol drinking (0.2%) and tobacco smoking in Vietnamese women aged 15+ (1.7%) in 2010 [18] and it was a similar observation in the 1990s [20]. The estimated prevalence of Hepatitis C virus infection was very low (0.5%) in rural areas [19]. There was also a very low prevalence (4.8%) of overweight among Vietnamese women. Therefore, Vietnamese women will be minimized risk of Liver Cirrhosis caused by alcoholism, smoking, Hepatitis C virus infection, and obesity. From 2005 to 2018, nutrition and diet, living and working environments have been improving which might be explained why there was a significantly decreased trend of mortality from the disease in the study population. In contrast, a significant increasing trend in men might be related to the increasing prevalence of harmful usage of alcohol from 25.5% in 2004 to 35.0% in 2013 [21].

The present study has several strengths, including long time of mortality registration from 2005 to 2018 to examine time trend of the disease; a large number of mortality cases was reported for both men and women; the covered study population was for the entire

Lang Son province with good healthcare systems from communes to district and provincial health facilities; mortality registration was actively and yearly done by professional health workers; the average population by each of 226 communes was updated for every year that allows us to estimate the age-standardized mortality rates by genders and for each year [16,17]. In addition, the quality of mortality registration in Viet Nam has been validated [22-24] to be performed well which will be feasible, reliable, and practical to develop annual local and national mortality databases of mortality to identify priority public health problems and to create planning timely actions in general and in controlling Liver Cirrhosis in particular. Based on these favorable research conditions, we can observe a real problem of the disease and add some new pieces of knowledge for further elimination of this preventable health threat in our society.

Liver Cirrhosis was a serious public health problem at the disadvantaged highland in Viet Nam of the present study population and that was consistent with findings in the world. There were 1.32 million deaths due to Liver Cirrhosis reported in 2017, with 440,000 deaths in women and 883,000 deaths in men. The burden of disease has been increased from 1990 to 2017. That is, the estimated deaths due to Liver Cirrhosis were responsible for about 2.4% of total deaths in the world in 2017 compared with 1.9% in 1990 [25]. In this study, we found that mortality due to cirrhosis was 5.3% of total deaths during 2005-2018 in the Lang Son province that was over doubled than the world estimation. There has been no systematic nationwide screening for Liver Cirrhosis in Viet Nam, especially in the mountain areas, and no nationwide comprehensive response to the disease.

The present study has certain limitations that include i) missing data for the year 2009-2010; ii) there is no available data of histopathological confirmation of Liver Cirrhosis, and iii) there is not the available data of lifestyle and environmental factors related to the disease. Despite these limitations, the present findings warrant further studies to identify risk factors for implementing primary prevention and secondary prevention in the community.

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There was no support.

## Conflicting Interest

There are no conflicts of interest to disclose.

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