Proportion of Pancreatic Necrosis among Patients with Acute Pancreatitis and Association between High-Density Lipoprotein (HDL Cholesterol) and Pancreatic Necrosis – A Prospective Observational Study from Kerala, South India

Jayas Siby[1], Preetha S.[2], Sindhu R.S.[3]

[1, 2] Department of General Surgery, Government Medical College, Thiruvananthapuram, Kerala, India.
[3] Department of Surgical Gastroenterology, Government Medical College, Thiruvananthapuram, Kerala, India.

ABSTRACT

BACKGROUND

Acute pancreatitis is a very common disease and severe acute pancreatitis is life threatening and needs early identification. Current severity predicting indices in acute pancreatitis are cumbersome. There have been previous reports of low HDL cholesterol in life threatening acute pancreatitis. Previous studies in this regard were done in a single ethnicity population and needed to be validated in other ethnic groups. We wanted to estimate the proportion of pancreatic necrosis among the patients with acute pancreatitis attending Government Medical College, Thiruvananthapuram. We also wanted to compare the mean HDL values in those who developed pancreatic necrosis and those who didn't develop pancreatic necrosis and evaluate the association between HDL value measured 48 – 72 hours of onset of symptoms and pancreatic necrosis.

METHODS

This was a prospective observational study conducted among 271 patients diagnosed with acute pancreatitis in Government Medical College Hospital, Thiruvananthapuram. Consecutive sampling method was used.

RESULTS

There were 42 cases of pancreatic necrosis out of 271 cases. The mean HDL of those patients with pancreatic necrosis was found to be less than those without necrosis ($P < 0.001$). Mean HDL value among those having pancreatic necrosis was 17.7 whereas those without necrosis was 34.9.

CONCLUSIONS

Proportion of pancreatic necrosis was 15.5 %. The mean HDL measured at 48 hours of symptom onset among the necrotising pancreatitis patients was significantly low when compared to the non-necrotic group (17.7 vs 34.9). All the patients with pancreatic necrosis had their HDL less than 40. Thus, an inference that low HDL at 48 hours of symptom onset was associated with higher incidence of pancreatic necrosis and severe pancreatitis could be made.

KEYWORDS

Pancreatitis, HDL, Pancreatic Necrosis

Corresponding Author:
Dr. Preetha S.,
Department of General Surgery,
Government Medical College,
Thiruvananthapuram, Kerala, India.
E-mail: arulakam69@gmail.com

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BACKGROUND

Acute pancreatitis is a very common disease which causes significant morbidity and mortality.[1,2] Its clinical course can vary from mild abdominal pain to organ failure and death.[1,2] It is one of the most common diseases causing morbidity getting admitted in surgical wards. It causes serious concern to the victims due to the pain, chance of recurrence, potential for developing complications and even death.

The incidence of acute pancreatitis is on the rise. One of the major reasons may be the rise in alcohol consumption.

Severe form of pancreatitis involving pancreatic necrosis and organ failure can be lethal and life threatening at times. These patients require intensive resuscitation and monitoring. At the same time patients with mild pancreatitis get their symptoms relieved without much active intervention. Thus, identifying the potential candidates going into complications is important which helps in treating the patients who need it most. It also helps in better judicious utilisation of resources.

There are so many scoring systems for assessing and predicting the severity of pancreatitis. Many of them are cumbersome and involves multiple parameters. This led to the search for easily available parameter which is associated with severe pancreatitis. HDL cholesterol measurement to predict severity of pancreatitis is a cheaper and effective way, in terms of cost involved and availability. It can be easily done in any basic biochemistry lab.

Immunological reaction has been proposed as the mechanism for development of acute pancreatitis.[3,4] There has been previous reports of low HDL cholesterol in life threatening acute pancreatitis.[5–10] This may be due to the fact that decreased HDL cholesterol has been observed in immune activation conditions previously. It has been proposed that HDL cholesterol has anti-inflammatory and anti-apoptotic activities by researchers

Ovia et al. has suggested through his study that acute pancreatitis involves immune suppression and persistent inflammation through immune mechanisms like impaired NFκB activation and enhanced p38 activation.[3] Catapano et al. has pointed the role of HDL cholesterol in innate and adaptive immunity.[11] They have suggested that HDL cholesterol will undergo changes in structure and function in sepsis and severe disease and decreased HDL will influence the cholesterol availability to immune cells. These changes are associated with poor prognosis in sepsis.

Sviridov et al. has studied the anti-inflammatory role of HDL and discusses the fundamental principles for designing lipoprotein mimetics.[12] Yvan Charvet et al. has demonstrated that all HDLs can supress inflammation especially toll like receptor 4 mediated inflammatory response.[13] Bugdaci et al. has reported in his study that there was a statistically significant relation between HDL cholesterol and severity of acute pancreatitis.[6] They reported significant correlation between low HDL cholesterol and acute pancreatitis. Jahangir khan et al. has reported low levels of HDL cholesterol in acute alcoholic pancreatitis patients during hospital stay, but hey could not establish the association between low HDL and severity of disease.[7] Jahangir et al. in his other study reports statistically significant lower HDL values in severe acute pancreatitis.[8] But he could establish this only in alcohol induced pancreatitis. Peng et al. in his study has reported significantly lower HDL levels in severe form of acute pancreatitis patients, and reports HDL cholesterol as a marker for organ failure and severity along with apoA1.[9] Unal et al. has suggested that decreased HDL has a role in pathogenesis of acute pancreatitis.[10] Zhang et al. has reported that decreased HDL cholesterol in severe acute pancreatitis can predict pancreatic necrosis, persistent organ failure and mortality in acute pancreatitis[5] in Chinese population.

Evidences for correlation between HDL cholesterol and pancreatitis has not been fully established. Few previous studies have found association between low HDL cholesterol and severity of acute pancreatitis. One study (Zhang et al.) has given evidence that decreased HDL cholesterol in severe acute pancreatitis can predict pancreatic necrosis, persistent organ failure and mortality in acute pancreatitis.[5] But that was done in a single ethnicity population and needs to be validated in other ethnic groups.

This encouraged us to do this study in our setting. In this study we are trying to find the proportion of pancreatic necrosis among acute pancreatitis cases and to establish the relation between HDL cholesterol measured 48 – 72 hours of onset of abdominal pain and pancreatic necrosis in patients.

Objectives

1. The primary objective of this study was to estimate the proportion of pancreatic necrosis among the patients with acute pancreatitis.
2. Secondary objectives were to compare the mean HDL values in those who developed pancreatic necrosis and those who didn't develop pancreatic necrosis among the patients with acute pancreatitis and to find the association between HDL value measured 48 – 72 hours of onset of symptoms and pancreatic necrosis among the patients with acute pancreatitis.

METHODS

It was a Prospective observational study conducted from June 2018 to June 2019 involving the patients admitted with the diagnosis of acute pancreatitis as determined by the treating surgeon with abdominal pain + anyone of the following - elevated serum amylase and lipase (≥ 3 times of upper limit of normal) or USG / CT suggestive of acute pancreatitis in the age group of 18 – 80 yrs. Inclusion Criteria were diagnosis of acute pancreatitis, 18 – 80 years' age and consent for participating in the study. Traumatic pancreatitis**,** prior hyperlipidaemia**,** patients on other drugs which could interfere with lipid metabolism (statins, thiazide diuretics, fibrates, estrogen analogues, tamoxifen, protease inhibitors, isotretinoin, A-blockers, and amiodarone) pancreatic tumours and anatomic malformations of pancreas were excluded from the study. Every consecutive case who fulfilled inclusion criteria and who gave consent was included in the study population until the sample size was met.

Sample size was calculated as 271 by taking the proportion of pancreatic necrosis and death from Zhang et al.[5] study.

All patients got a USG abdomen done within 24 hours of admission along with other routine investigations and a lipid profile at 48 hours of onset of symptoms. All patients received the standard treatment which was followed in the department. Contrast-Enhanced computed tomography (CECT) was taken for all patients who were not improving symptomatically after 48 hours.

Patients with no evidence of pancreatic necrosis in the initial CT, but continued to worsen or developed the signs of complications were taken for repeat CT. On the basis of CT and other investigations, patients were categorised into two groups (those with pancreatic necrosis and those without pancreatic necrosis). All patients were followed up till discharge/death. Hard copies of consent forms were kept with primary researcher.

Ethical Considerations

Institutional ethical committee clearance was obtained. Informed consent obtained from the participants. Confidentiality was ensured and maintained throughout the study. No additional financial burden over the patient was ensured. The investigations required for the study were done free of cost from the hospital lab.

Statistical Analysis

Data entered in excel sheets and analysed using SPSS version 16. All quantitative variables were expressed as mean and standard deviation and all qualitative variables were expressed as proportion. Baseline characteristics of the two groups were compared with the student t test. The association between HDL cholesterol and pancreatitis was tested using t test and chi square test. HDL values less than 40 were considered as low and above 40 were considered as normal/high.

RESULTS

Age Distribution

Acute pancreatitis occurred in all age groups. Maximum incidence was in 31 - 40 years' age group (33.9 %), next is 41 - 50 years (22.5 %). Together 54.4 % cases belonged to age group 31 - 50 years and middle age group. There were only 3 cases (1.1 %) who were more than 70 years of age and only 4 cases (1.5 %) who were below 20 years of age. Mean age was 42 with standard deviation of 12.3.

Sex Distribution

Out of the 271 cases, 247 (91.1 %) were males and only 24 (8.9 %) were females.

Aetiology

Out of 271 cases, aetiology of 219(80.8 %) were found to be alcohol. 39 (14.4 %) patients had Gall stones as the aaetiology of acute pancreatitis. There were 2 patients (0.7 %) who developed post Endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis and 2 patients (0.7 %) who developed drug induced pancreatitis. There was no specific aetiology identified (idiopathic) in 9 patients (3.3 %)

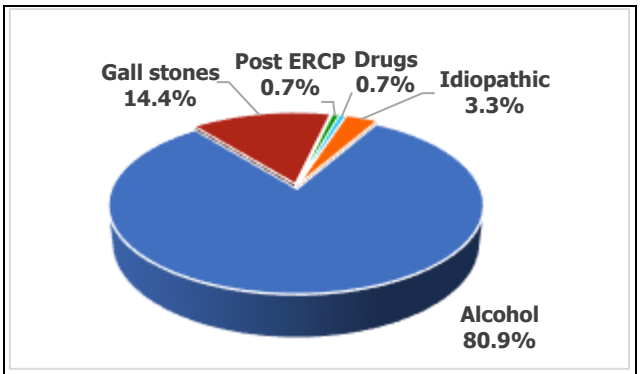

Figure 1. Aaetiology of Acute Pancreatitis

Aetiology and Sex Distribution

100 % of alcoholic pancreatitis occurred in males. Out of 39 gall stone pancreatitis, 23 (58.9 %) were males and 16 (41 %) were females. Out of the 2 Post ERCP cases, 1 was male and 1 was female. There was only 2 drug induced pancreatitis, both of which were females. Out of the 9 idiopathic cases, 2 (22.2 %) were males and 7 (77.7 %) were females.

Survival Status

5 out of 271 (1.8 %) died due to the disease.

Lipid Profile Distribution

Mean value of HDL was 32.3 with a standard deviation of 14.8. The lowest value of HDL recorded was 8 and the highest value was 82. The mean value of LDL was 97.74 with a standard deviation of 37.35. The mean value of triglycerides was 127.8 with a standard deviation of 63.3. Mean value of total cholesterol was 162.2 with standard deviation of 42.4.

Frequency of Necrosis

Out of the 271 participants in the study, 42 (15.5 %) patients developed pancreatic necrosis while 229 (84.5 %) patients didn't develop any pancreatic necrosis.

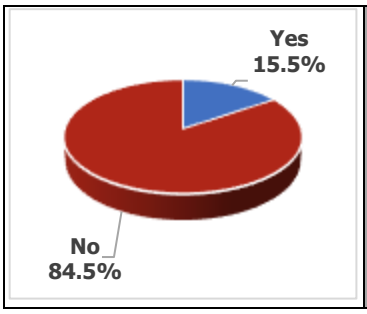

Figure 2. Frequency of Necrosis

Age Wise Distribution of Pancreatic Necrosis

2 out of 3 patients above 70 years had pancreatic necrosis**.** 13 out of 61 patients in 41-50 years' age group (21.3 %) had necrosis, which is the highest incidence. The mean age of patients with necrosis was 42.8 and who didn't have necrosis was 41.8, for which no statistical significance was found (P value – 0.646).

Sex Distribution of Pancreatic Necrosis

37 out of 247 (15.0 %) males developed pancreatic necrosis**.** 5 out of 24 (20.8 %) females developed pancreatic necrosis**.** However, this was not found to be statistically significant.

Aetiology Wise Distribution of Pancreatic Necrosis

There was 15.1 % incidence of necrosis among alcohol induced pancreatitis, 20.5 % incidence among gall stone induced pancreatitis, 50 % incidence among drug induced pancreatitis. There was 0 incidence of necrosis among post ERCP pancreatitis and idiopathic pancreatitis. These are not found to be statistically significant.

Aetiology	Necrosis				Total	
	Yes		No			
	N	%	N	%	N	%
Alcohol	33	15.1	186	84.9	219	100.0
Gall stones	8	20.5	31	79.5	39	100.0
Post ERCP	0	0.0	2	100.0	2	100.0
Drugs	1	50.0	1	50.0	2	100.0
Idiopathic	0	0.0	9	100.0	9	100.0
Total	**42**	**15.5**	**229**	**84.5**	**271**	**100.0**

Table 1. Aetiology Wise Distribution of Pancreatic Necrosis

$\chi^2 = 4.615$, df = 4, P = 0.329

Pancreatic Necrosis and Survival Status

Of the total pancreatic necrosis cases, 5 expired. All the expired patients were found to have pancreatic necrosis. Among the patients with no evidence of pancreatic necrosis, all survived.

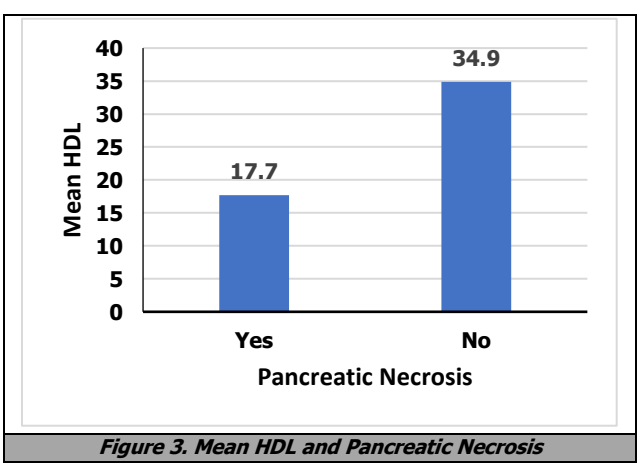

Figure 3. Mean HDL and Pancreatic Necrosis

Mean HDL among patients with pancreatic necrosis was 17.7 with a standard deviation of 6.5. Mean HDL among patients without pancreatic necrosis was 34.9. This relation was statistically significant (P = < 0.001).

HDL	Necrosis				Total	
	Yes		No			
	N	%	N	%	N	%
≤ 40	42	100.0	160	69.9	202	74.5
> 40	0	0.0	69	30.1	69	25.5
Total	**42**	**100.0**	**229**	**100.0**	**271**	**100.0**

Table 2. HDL Values and Pancreatitis

$\chi^2 = 16.978$, df = 1, P < 0.001

All the necrotising pancreatitis cases had HDL values below 40. On applying chi square test this was found to be significant (P < 0.001). 69.6 % of non-necrotising pancreatitis also had HDL less than 40.

LDL and Pancreatic Necrosis

Mean LDL among patients with pancreatic necrosis was 91.1 and those without pancreatic necrosis was 112.1. This was not statistically significant.

Triglycerides and Pancreatic Necrosis

Mean value of triglycerides among patients with pancreatic necrosis was 151.7 and among those without necrosis was 123.5. P value for this relation was 0.008.

Total Cholesterol and Pancreatic Necrosis

Mean value of total cholesterol among patients with pancreatic necrosis was 166.6 and in non-necrotic group 161.4. There was no statistically significant difference found. (P value – 0.464).

DISCUSSION

A total of 271 patients were included in the study based on inclusion and exclusion criteria. Data was entered in Microsoft excel and analysed with SPSS software version 16.

Epidemiology and Aetiology of Pancreatitis

In this study the maximum incidence of the disease was in 31- 50 years' age group, which was consistent with existing literature. Mean age was 42 years. There was clear male predominance in the incidence of acute pancreatitis. 91.1 % of the total cases were males. Existing literature says incidence was almost same in males and females.[14] We have obtained a conflicting data on sex distribution. This was probably due the aetiological factors. Aetiology of 80.8 % cases was alcohol. In Kerala prevalence of alcoholism was generally low in females.

Thus, alcoholic pancreatitis exclusively reported in males in this study. This explains the abnormally high sex ratio in favour of males in acute pancreatitis. Next common aetiology was gall stones which accounts for 14.4 % cases. This warrants further studies to know the pattern of alcohol consumption in Keralites and factors controlling alcohol induced pancreatitis as well as to know about any genetic or ethnic basis for such a high incidence of alcohol induced pancreatitis in Kerala. When going through this data it

should also come into one's mind the fact that tropical pancreatitis has an exceptionally high incidence in Kerala.

Pancreatic Necrosis

42 patients among the 271, i.e. 15.5 % had pancreatic necrosis. According to a metanalysis by Petrov et al. in which 14 studies were analysed, incidence of pancreatic necrosis was 21 %.[15] Our data has slightly less but comparable incidence with existing literature with regard to pancreatic necrosis. An analysis of incidence of pancreatic necrosis among different aetiologies was done, however this was not found to be statistically significant (P = 0.329). Thus, aetiology is not a factor that decides development of pancreatic necrosis and complications.

Only 5 patients (1.8 %) died of pancreatitis among the 271. This is far below the mortality rate in existing literature which varies between 5 - 32 %,[16,15] probably due to early diagnosis and initiation of resuscitation, and advancements in critical care. It may be also due to very high incidence of alcohol induced mild pancreatitis. All the expired 5 patients had pancreatic necrosis. Thus, pancreatitis without necrosis is unlikely to go into life threatening complications. Thus, identification of potential candidates for development of pancreatic necrosis is important.

HDL and Pancreatic Necrosis

The mean HDL of those patients with pancreatic necrosis was found to be less than those without necrosis. Mean HDL value among those having pancreatic necrosis was 17.7, whereas those without necrosis was 34.9. This was found to be statistically significant with P < 0.001. Another chi square test showed that all the patients with pancreatic necrosis had low HDL value (less than 40). This was also found to be statistically significant (P < 0.001). The reasons for this were said to be immunological. HDL is also said to be an anti-inflammatory marker and is observed to be decreased in sepsis.

The mean triglyceride value among pancreatic necrosis group was found to be higher than non-necrosis group. This was statistically significant (P = 0.008). The correlation between higher triglyceride values and disease severity in acute pancreatitis has been shown in multiple studies conducted in different ethnic groups.[17-19] The findings from this study was in concordance with those studies which suggest higher triglyceride values associated with more severe pancreatitis.

However, the relations with LDL and Total cholesterol were not found to be significant. Thus, HDL cholesterol can be used a marker for identifying patients who are potential candidates for developing pancreatic necrosis. This will be far easier than the existing severity scoring systems. HDL done 48 hours after the symptom onset can thus help in focussing on patients who are likely to go into complications. This is important because the incidence of pancreatitis is on the rise and vast majority are self-limiting and the rest of the cases which develops complications needs active intervention to prevent death. We suggest using HDL as a marker to identify severe pancreatitis.

CONCLUSIONS

In this study, the proportion of pancreatic necrosis among acute pancreatitis was 15.5 %. The mortality due to pancreatitis was only 1.8 % in this study, far below the data from literature. This may be due to early detection and initiation of resuscitation, better critical care facilities or even due to the large number of alcohol induced mild pancreatitis. The mean HDL measured at 48 hours of symptom onset among the necrotising pancreatitis patients was significantly low when compared to the non-necrotic group (17.7 vs 34.9). All the patients with pancreatic necrosis had their HDL less than 40. Thus, an inference that low HDL at 48 hours of symptom onset was associated with higher incidence of pancreatic necrosis and prediction of severe pancreatitis could be made. This could be a useful biochemical test to identify those patients who are likely to go into complications and help us to focus on those patients. We hope that more studies to establish this relationship between HDL and pancreatic necrosis will come in the future.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
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