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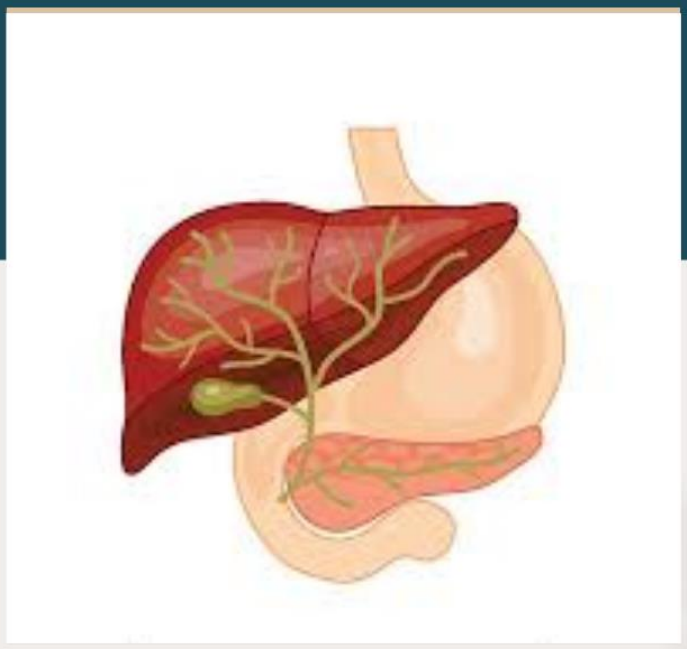

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PAKISTAN JOURNAL OF GASTROENTEROLOGY

Editorial

Hepatitis C elimination by 2030: Are we on the road to miss the target ?

Prof Ghias Un Nabi Tayyab

Post Graduate Medical Institute, Ameer ud Din Medical College

Hepatitis C virus infection represents a major global health concern, with Pakistan estimated to have the highest prevalence worldwide, affecting over 12 million individuals.[1] The historical spread of HCV in Pakistan started with mass vaccination of the population for smallpox but later on is attributed to various factors, including unsafe medical practices, contaminated injections, and blood transfusions.[2] Initially recognized as non-B chronic hepatitis, HCV was identified as a leading cause of chronic liver disease, often leading to cirrhosis, liver failure, and hepatocellular carcinoma. We recognize more than 6 genotypes of hepatitis C virus, and in Pakistan, genotype 3 has been the most prevalent one.[3] In the 90s and first decade of the 2000s, people were presenting with blood vomiting, ascites, and subsequent liver failure, and the number of people requiring liver transplants out-matched the available facilities. Lots of people died in their late 30s and mid-40s, the most productive age of humans, because of liver failure. From 2010 onwards, we saw a rapid increase of hepatocellular carcinoma arising out of chronic hepatitis C patients suffering from advanced liver fibrosis.[4]

The treatment of hepatitis C underwent a significant transformation from the 1990s until 2015. During this period, the cornerstone of therapy consisted of interferons combined with ribavirin. However, this approach was characterized by limited efficacy and a substantial burden of adverse effects.[5] Treatment regimens typically spanned 6 to 12 months, contributing to the considerable cost associated with these therapies. While public health departments implemented hepatitis control programs, access to these medications remained restricted, often necessitating patients to secure treatment through private resources. It is estimated that between 1995 and 2015, approximately 500,000 patients received interferon-based treatment, with a reported sustained virological response (SVR) rate of approximately 30%. National hepatitis control programs primarily concentrated on hepatitis B vaccination as a preventative measure and on raising public awareness regarding hepatitis B and C infection.

The landscape of hepatitis C treatment shifted dramatically with the initial publication in 2014 of research highlighting the safety and efficacy of directly acting agents (DAAs).[6] These compounds, belonging to diverse categories, demonstrated significant promise. Combination therapies involving DAAs proved highly effective and required substantially shorter treatment durations. Furthermore, these regimens exhibited pangenotypic activity, rendering them effective against all hepatitis C genotypes, and could be administered at all stages of disease progression.[7] Initially recommended for individuals aged 18 and above, DAAs are now considered safe and effective across all age groups, including during pregnancy.[8] Although DAA-based therapy initially posed a significant financial burden in many

countries,[9] collaborative initiatives involving the World Health Organization (WHO)[10] and pharmaceutical companies, such as Gilead, have facilitated the provision of more affordable treatment options in high-prevalence regions, such as Egypt and Pakistan.

Pakistan's endeavors to combat Hepatitis C demonstrate a complex interplay of progress and persistent challenges. The nation's commitment is evident in the development and subsequent revision of its National Hepatitis Strategic Framework (NHSF), culminating in the ambitious goal of eliminating Hepatitis C infection by 2030. Following the devolution of healthcare services in 2010, provincial authorities were tasked with formulating localized strategies, allocating resources, and integrating treatment protocols within existing healthcare systems. This decentralized approach, while empowering provinces, necessitates consistent and equitable implementation across the nation.

Initial progress under the 2017-2022 NHSF was notable, particularly in Punjab, where the enactment of the Punjab Hepatitis Control Act and the Safe Blood Transfusion Act, coupled with policies promoting safe waste disposal and the use of auto-destructible syringes, established a robust regulatory framework. Furthermore, substantial investments in infrastructure, including the establishment of over 200 hepatitis treatment centers, specialized gastroenterology units, and a dedicated liver transplant hospital, significantly enhanced treatment capacity. The creation of a national dashboard and interlinked clinics facilitated data management and streamlined patient care. Complementing these efforts, the College of Physicians and Surgeons, Pakistan, implemented specialized training programs to augment the pool of qualified healthcare professionals. The domestic pharmaceutical industry played a crucial role by providing directly acting agents (DAAs) at competitive prices, a key factor in expanding treatment access. However, the lack of comparable engagement from diagnostic firms, resulting in persistently high prices for PCR diagnostics, presents a significant obstacle. Technical advisory groups at both national and provincial levels formulated treatment guidelines for HCV and HBV infections, further contributing to standardized care .[11] While Punjab's early adoption of these measures provided a valuable model for other provinces, the observed disparities in implementation timelines underscore the critical need for more uniform and equitable progress across the nation .[12] The political transition of 2018, compounded by the unforeseen challenges of the 2019 COVID-19 pandemic, significantly disrupted program momentum, resulting in the diversion of crucial resources and a shift in public health priorities. Despite initial successes in providing treatment to approximately 1.6 million individuals between 2017 and 2019, subsequent treatment rates experienced a decline, primarily attributable to shortages in both diagnostic resources and essential medications. During this period, a substantial proportion of patients independently sought and financed their own treatment regimens. It is estimated that by 2022, more than 2.2 million of people got the treatment, either through public health programs or from their own resources. The current viremic rate stands at 54%, highlighting a substantial reduction in the actual patient pool. Consequently, the program's strategic focus has shifted towards the more complex and resource-intensive endeavor of identifying and treating the undiagnosed population, a task that necessitates the development and implementation of innovative and targeted strategies. It is hypothesized that a significant proportion of individuals aware of their

infection status have already received treatment, leaving a substantial reservoir of undiagnosed cases within the community, thereby posing a continued public health challenge .[13]

Pakistan's response to Hepatitis C has yielded commendable achievements, particularly in infrastructure development and treatment provision. However, the enduring challenge of high diagnostic costs, coupled with the disruptive impact of external factors and the imperative to reach undiagnosed individuals, necessitates a renewed and intensified effort. Addressing the affordability of diagnostics and implementing targeted interventions to identify and treat the "missing millions" are critical for the realization of the 2030 elimination target.

Following the COVID-19 pandemic, a renewed emphasis on hepatitis control activities was expected. However, ongoing political and economic instability within the nation has thus far precluded this anticipated resurgence, remaining an unrealized objective. Various modeling studies have consistently demonstrated that a failure to address the current hepatitis C situation will have significant repercussions for both the health economy and the broader macroeconomic context.

The second iteration of Pakistan's National Hepatitis Strategic Framework (2024-2030) has been initiated with a budget allocation of PKR 68.25 billion, sourced from the Public Sector Development Program .[14] Provincial governments are tasked with actively mobilizing resources to support the diverse components of the national hepatitis control strategy. Strategic discussions have revealed differing perspectives, with public health departments advocating for macro-elimination strategies, while non-governmental organizations (NGOs) are prioritizing micro-elimination approaches, frequently leveraging media and social media platforms to enhance public visibility. While the micro-elimination approach may possess an inherent appeal, its implementation at the national level presents significant cost constraints. Consequently, a nationwide macro-elimination strategy is deemed essential, requiring a multi-faceted communication approach encompassing mobile phone messaging campaigns, print and electronic media outreach, public advocacy initiatives, robust contact tracing mechanisms, and effective linkage to care through established public and private healthcare infrastructure. Although the elimination of HCV by 2030 remains a theoretically attainable objective, a substantial augmentation of current efforts is imperative to successfully meet this ambitious target.

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PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Gastrointestinal and hepatobiliary manifestations of COVID-19 infection: A single canter study from Pakistan

Sami Ullah Mumtaz[1], Rabiah Haque[4], Tayyeba Komal[2], Somia Iqtadar[3], Zafar Niaz[3], Sajid Abaidullah[3]

1. **Narowal Medical College, DHQ Teaching Hospital, Narowal.**
2. **Service Institute of Medical Science Lahore.**
3. **King Edward Medical University Lahore.**
4. **Shaukat Khanum Memorial Cancer Hospital, Lahore.**

ABSTRACT

Background: Coronavirus disease was a global challenge affecting around 229 countries with over 700 million confirmed cases with significant morbidity and mortality.
OBJECTIVE: To determine the prevalence and spectrum of gastrointestinal and hepatobiliary manifestations in COVID-19 patients, including liver function test abnormalities and clinical features, within the Pakistani population.

Methodology: This was a cross-sectional study conducted at North Medical Ward, Mayo Hospital, Lahore for three months. After ethical approval of the study, 200 COVID-19 RT-PCR positive cases of ages 15 to 80 years were included in the study. Complete history & examination regarding hepatobiliary symptoms were noted. Liver function tests & prothrombin time were sent to pathology laboratory & results were noted. Data was analyzed using SPSS-26. Chi-square tests and t-tests were used to compare categorical and continuous variables, respectively. Quantitative variables like age, bilirubin, Aminotransferases & Prothrombin time were taken as mean ± standard deviation. Qualitative variables like gender, hepatobiliary symptoms were taken as frequency and percentages.

Results: The most common symptom at presentation was diarrhea 30 (15.0%) followed by fatigue, pruritic and anorexia 17 (8.5%), nausea, vomiting and abdominal pain 15 (7.5%), body petechiae & purpura in 13(6.5%), Right hypochondrial pain 11(5.5%) & Hiccup and dark colour urine 1(0.5%). On laboratory findings,17(8.5%) patients had elevated bilirubin levels while AST was raised in 79(39.5%) of cases, ALT in 23(11.5%), Alkaline phosphatase in 6(3.0%), GGT in 95(47.5%) of cases. 8 (4.0%) cases showed decrease albumin level and 12(6.0%) cases had prolonged PT levels.

Conclusion: Gastrointestinal and Hepatobiliary manifestations are frequent in COVID-19 patients and should be closely monitored. Recognition of these symptoms could help mitigate delays in diagnosis and treatment, particularly in asymptomatic or non-respiratory patients.

Keywords: COVID-19, Pandemic, Liver Function Tests, Hepatobiliary, Manifestations.

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Corresponding Author: Sami Ullah Mumtaz **Email: drsumumtaz@gmail.com**

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INTRODUCTION

A novel coronavirus disease (COVID-19) outbreak was reported in seafood market in Wuhan city of China since end of December 2019, which has subsequently affected 229 countries so far.[1,2] Since then, this disease has infected almost 700 million people worldwide. In Pakistan, it has been known to cause over 1.5 million infections. While respiratory symptoms are predominant, hepatobiliary manifestations have also been reported but remain under-explored in local studies.[3]

In general, COVID-19 is an acute resolved disease but severe disease onset might result in death due to massive alveolar damage and progressive respiratory failure. [4] Although most coronavirus infections amount for mild respiratory illnesses, expression of the ACE2 gene a receptor for the SARS-CoV-2 virus with in the gastrointestinal tract suggests the digestive system is a potential targeted infection for COVID-19 making patients with an affected hepatobiliary system susceptible to this novel infection. Very limited data are available on the prevalence of COVID-19 among patients with pancreatic or biliary conditions although pancreatic manifestations of the disease are rare.[5]
The pathogen responsible for COVID-19 disease has been isolated from a family of enveloped, positive sense RNA viruses, characterized by club shaped spikes that project from their surface, an unusually large RNA genome and a unique replication strategy.[7] Multiple trials are going on to discover definitive treatment modalities of this novel disease as well as for its vaccine. The pandemic of COVID-19, caused by the virus SARS-CoV-2 can be either asymptomatic or with mild to moderate symptoms leading to acute respiratory distress syndrome. Common symptoms of the disease include fever, flu, sore throat, cough, myalgia & less common symptoms are sputum production, & headache. Gastrointestinal and hepatobiliary involvement can range from asymptomatic liver enzyme elevation to more pronounced clinical manifestations. Identifying such patterns, especially in the Pakistani population is vital for guiding clinical management and understanding the regional impact of the disease. More specifically the hepatobiliary symptoms include anorexia, malaise, abdominal pain, nausea, vomiting, dark colored urine, clay-colored stools, pruritis & diarrhea. Jaundice has also been reported.[6] Liver chemistry abnormalities are also common and include elevation of aspartate transferase (AST), alanine transferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT) and total bilirubin.[6]

The hepatobiliary system can be affected through multiple mechanisms, including direct viral cytopathic effects, immune dysregulation, and drug-induced liver injury. This study aims to explore the prevalence, clinical features, and laboratory

abnormalities associated with hepatobiliary involvement in COVID-19 patients in Pakistan. [7]

In this study we will determine the frequency of these symptoms in our population as little local data is available about the disease & diagnosis can be missed due to non-respiratory symptoms.

OBJECTIVE:

To determine the prevalence and spectrum of gastrointestinal and hepatobiliary manifestations in COVID-19 patients, including liver function test abnormalities and clinical features, within the Pakistani population.

METHODOLOGY:

This was a cross-sectional study, conducted at the North Medical Ward, Mayo Hospital, Corona isolation ward, Lahore between 1st June and 31st August 2020. After ethical approval of the study from institutional review board, King Edward Medical University Lahore, 200 patients were enrolled with informed consent. Patients of ages 15 to 80 years of either sex with COVID PCR positive status were included in the study. All patients with ages below 15 years & above 80 years & prior liver or biliary diseases like cholangiocarcinoma, acute or chronic hepatitis, chronic liver disease etc. were excluded. Demographic details including name, age, gender, address & contact number were recoded. Complete history & examination of each enrolled patient regarding hepatobiliary symptoms was done & recorded in a predesigned proforma. Then 2ml venous blood sample of every covid-19 positive patient was sent, each for Liver function tests & prothrombin time (PT) to Pathology laboratory. These tests results were then recorded in the predesigned proforma in standard SI Units. Data was analyzed using SPSS-26. Chi-square tests and t-tests were used to compare categorical and continuous variables, respectively. Quantitative variables like age, bilirubin, Aminotransferases, Alkaline phosphatase, gamma glutamyl transferase (GGT), albumin & PT were recorded as mean ± standard deviation. Qualitative variables like sex and hepatobiliary symptoms were taken as frequency and percentages.

RESULTS:

The mean age of patients positive for COVID-19 was 34.16±16.70 years. There were 94 (47%) males and 106 (53%) females. We found that 46(23.0%) Covid positive patients had hepatobiliary symptoms without any respiratory feature, while 14(7.0%) cases had both hepatobiliary and respiratory symptoms.

The most common hepatobiliary symptom at presentation was diarrhea 30 (15.0%). Others include fatigue, pruritic and anorexia 17 (8.5%), nausea, vomiting and abdominal pain 15 (7.5%), body petechiae & purpura in 13(6.5%), Right hypochondrial pain 11(5.5%) & Hiccup and dark color urine 1(0.5%). No patient presented with jaundice or clay colored stool. (Table 1) Among 200,113(56.5%) patients had non-hepatobiliary symptoms (Table 1)

Table1: Gastrointestinal and hepatobiliary manifestation of COVID-19 Infection.

Symptoms	Percentage (%)
Diarrhea	30 (15.0%)
Nausea & vomiting, Abdominal Pain	15 (7.5%)
Right hypochondrial pain	11 (5.5%)
Hiccup, Fatigue, Pruritis, Anorexia	17 (8.5%)
Body Petechiae, Purpura,	13 (6.5%)
Dark Colored Urine	1 (0.5%)
Clay colored stools, Jaundice	0(0.0%)
Non-hepatobiliary Symptoms	113(56.5%)

On laboratory findings, mean bilirubin level of patients was 0.77±0.39 IU/ml, mean AST and ALT were 42.3±22.7 & 43.6±21.9, respectively, mean alkaline phosphate was 95.3±30.0, mean GGT was 46.4±33.7, mean total protein level was 6.7±0.4 mg/dl, mean albumin was 3.8±0.4 mg/dl and mean PT of patients was 11.85±1.4 sec. 17(8.5%) patients had elevated bilirubin levels while AST was raised in 79(39.5%) of cases, ALT in 23(11.5%), Alkaline phosphatase in 6(3.0%), GGT in 95(47.5%) of cases. 8 (4.0%) cases showed decrease albumin level and 12(6.0%) cases had prolonged PT levels. (Table-2).

Table 2: Laboratory findings of COVID-19 Patients (LFTS & PT)

Lab test with Normal Values Range	Mean±SD	Normal	Abvove Normal	Below Normal
Bilirubin(0.3-1.2mg/dl)	0.77±0.3	183 (91.5%)	17(8.5%)	0 (0%)
AST(10-40IU/L)	42.3±22.7	121 (63.5%)	79 (39.5%)	0 (0%)
ALT(7-56IU/L)	43.6±21.9	177 (88.5%)	23 (11.5%)	0 (0%)
Alkaline phosphate(44-147IU/L)	95.3±30.0	194 (97.0%)	6 (3.0%)	0 (0%)
GGT(5-40 IU/L)	46.4±33.7	104 (52.0%)	95 (47.5%)	1 (0.5%)
Total Protein(6-8.3g/dL)	6.7±0.4	200 (100%)	0 (0%)	0 (0%)
Albumin(3.5-5.5g/dL)	3.8±0.4	192 (96.0%)	0 (0%)	8 (4.0%)
PT(11-13.5Sec)	11.85±1.48	141 (70.5%)	12 (6.0%)	47 (23.5%)

DISCUSSION:

In this study, we found that hepatobiliary manifestations are a common complaint in patients presenting with COVID-19. The purpose of the study was to detect these extra-pulmonary symptoms so that earlier treatment can be initiated to avoid any further complication.

In clinical practice, Covid positive patients mainly present with respiratory symptoms but evidence of damage to other organ systems have also been reported. Especially critical patients are susceptible to multiorgan damage [8]. In our study, patients also presented with hepatobiliary symptoms without respiratory symptoms. So, clinicians and gastroenterologists should pay attention to these extra pulmonary symptoms of Covid-19, as lesser attention to these initial findings can contribute to transmission inside family or community.[9]

By reviewing the literature, it was found that there are several reasons of Covid-19 to cause hepatobiliary symptoms. SARS-CoV-2 is similar to SARS-CoV and can bind to angiotensin converting enzyme 2 (ACE-2) receptors that causes liver damage by upregulation of ACE-2 expression in the liver tissue.[10] The high proportion of cases with liver injury suggests that hepatic dysfunction plays a critical role in multisystem organ dysfunction. It is caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells. It also damages digestive system directly or indirectly by an inflammatory process.[11]

Through different studies, it was found that viral nucleic acid is detected in stool samples of 53% of Covid positive patients.[12] In a study by Zhang and colleagues reported that the majority of fatal COVID-19 cases (up to 78%) had clinical evidence of liver injury. [13]

In the liver, single-cell transcriptome analysis from several studies (involving both human tissues and organoid cultures) has confirmed the presence of ACE2 receptor and TMPRSS2 in liver parenchymal cells and cholangiocytes.[14-16] Hepatic complications of COVID-19 may not be directly related to the infection itself but may be caused by the various therapies that are used to prevent or combat the disease. [17]

Shih AR and colleagues in their study found out that ischemic enterocolitis was the most common related gastrointestinal manifestation; consequence of COVID-19 and liver injury was related to

consequences of severe systemic viral infection.[18]

Liondthard S et.al concluded that COVID-19 causes Secondary Sclerosing Cholangitis in a substantial proportion of critically ill patients in contrast to our study where we didn't find any case of Secondary Sclerosing Cholangitis.[19]

In a study by Mushannen M on 161,689 patients with COVID-19 infections, 683 developed hepatobiliary complications possibly related to COVID-19 infection. They distributed these patients into different categories: 61 patients with cholangitis, 1 patient with acalculous cholecystitis, 5 patients with choledocholithiasis, 11 patients with hepatitis, 140 patients with steatosis, 22 patients with cirrhosis, 3 patients with acute liver failure, 29 patients with liver inflammation by imaging, 41 patients with hepatomegaly, and 370 patients with unspecified hepatobiliary disease. Of these, 6 patients died.[20]

There are certain limitations of our study. Firstly, this was a study with limited sample size and single centered that can affect reliability as well as generalizability. Secondly, we did not test for RNA or ACE2 levels in hepatocytes samples of Covid positive patients.

CONCLUSION

In conclusion gastrointestinal and hepatobiliary symptoms are not uncommon in patients with COVID-19. Patients having coronavirus disease can present only with gastric or hepatobiliary symptoms such as diarrhea, vomiting, nausea and abdominal pain without any respiratory symptoms; such patients' diagnosis may be delayed. So, attention should be given to these initial extra-pulmonary features to avoid disease progression & complications.

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Author's Contribution:

SUM: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
RH, TK, SI, ZN, SA: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Impact of HCV eradication on HBAIC in Genotype 3 Chronic HCV Diabetic Patients

Taha Tariq, Ayesha Waheed, Mohammad Rohaan Ajmal, Usman Akram, Umer Hayat

Department of Gastroenterology. Ghurki Trust Teaching Hospital / Lahore Medical & Dental College Lahore.

ABSTRACT

Objective: Hepatitis C Virus (HVC) is a global health concern. WHO estimated that it affects a 170 million people worldwide. In Pakistan, 6.8% of adult population exhibits presence of active disease. With the rise of DAAs especially Sofosbuvir and Velpatasvir, the ETR and SVR is remarkable. Patients who secure seroconversion following DAA treatment experience a drop in their HOMA-IR levels, in contrast to those who don't. It means that these are metabolic benefits of HCV eradication. Based on this hypothesis, we evaluated the benefit on HBAIC in patients achieving ETR.

Methods: the study sample comprised 100 type 2 diabetics who attended gastroenterology clinic at Ghurki Trust Teaching Hospital (GTTH), a tertiary care hospital in Lahore for treatment of HCV infection. All the confirmed type 2 diabetes cases on any therapy were included in the study sample. Data was analysed using SPSS Statistics version 24.

Results: Out of study sample of 100 patients, 100% achieved an end of treatment response (ETR). In our study, mean difference in fasting blood sugar (FBS) from baseline to ETR was found to be a decrease of 48.70 ± 22.20 mg/dL (p Value<0.05). Similarly, the mean difference RBS over the same duration showed a reduction of 98.00 ± 39.70 mg/dL (p value <0.05) Quite interestingly, HbA1c levels also showed a decline of mean difference of 1.10 ± 0.82% from baseline to the 3 months mark (p value<0.05)

Conclusion: Successful eradication of HCV does lead to improvement in Diabetes control in type 2DM.

Key words: Diabetes Mellitus, HCV, ETR, HBAIC, Sofosbuvir, Velpatasvir

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Corresponding Author: Taha Tariq **Email: tahatariq2201219@gmail.com**

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Introduction:

Hepatitis C Virus (HCV) is a global health problem with an estimated 170 million population of world, suffering from this and it leads to fatal complication of cirrhosis and hepatocellular carcinoma[1]. Developing countries, like Pakistan has an estimated prevalence of 6.8% making it more vulnerable to cirrhosis and its complications[2]. Interestingly the most common genotype of HCV is type 3 in Pakistan, which is claimed to be easier to treat as compared to other genotypes[3]. But already alarming figures of prevalence are further intensified when we observe an interplay between HCV and Diabetes Mellitus[4]. Diabetes is already very prevalent in Pakistan with almost every fourth adult is suffering from this disease[5]. The development of Type 2 DM is due to two fundamental disturbances: tissues like muscle, liver, and adipose becoming less responsive to insulin, and Pancreatic beta cells gradually losing their ability to produce required insulin in response to needs of body[6]. Genetic predispositions, environmental and lifestyle factors, notably poor diet, lack of physical activity, and resultant obesity, are critical contributors to its development[7]. Various studies believe that almost 70% of individuals with chronic HCV infection are at a risk of developing type 2 DM[8]. This is hypothesized due to alterations in insulin resistance and glucose metabolism mechanisms by the Hepatitis C Virus. Although the exact pathway of this connection is ambiguous but still then there is a possible role of HCV proteins in affecting insulin receptors and increasing the inflammatory cytokine levels[9]. In a local study on the prevalence of T2DM among HCV infected patients showed 26.42% prevalence of T2DM in patients infected with HCV[10]. In another study DM prevalence of 34.80% was seen in HCV infected individuals. Male patients showed a higher prevalence (40.40%) as compared to females (31.20%)[11].

The treatment regimen to treat chronic HCV has witnessed substantial advancements in past decade. Medications known as Direct-acting antivirals (DAAs) has remarkable success rates against all genotypes of HCV with fewer side effects as compared to previously used combination of Interferon and Ribavirin[12].The success of these antiviral agents in terms of better sustained virologic response (SVR) prompted researchers to see its impact on metabolic health of type 2 DM patients.[13]

A study done by Eslam et al, to look for positive relationship between HCV eradication and improvement in insulin sensitivity, showed that patients who secured an SVR following DAA treatment experienced a significant drop in HOMA-IR levels, as compared to those who didn't achieve SVR[14]. This highlights metabolic benefits of achieving HCV eradication but also provides a food for thought to prioritize HCV eradication as a preventative measure against development of T2DM. In work done globally it is now advocated that HCV infection stimulates the body's immune response, which then leads to secretion of pro-inflammatory cytokines like TNF-a and IL-6. These cytokines have an established role in modulating insulin signaling. When HCV eradication is achieved, levels of these cytokines drop significantly. This decline in pro-inflammatory cytokines then leads to increased insulin sensitivity, thus playing a role in reducing metabolic burden on body and DM[15 16].

We planned this study to investigate the potential of improvement of glycemic indices in Genotype 3 HCV patients who are using Sofosbuvir / Velpatasvir combo of DAA for achieving viral eradication.

Materials and methods

This study was done on 100 participants in Department of Gastroenterology and was a prospective cohort study for six months. Sample size of 100 was calculated by

assuming that 85% to 95% of the patients achieve improved glycaemic control after successful HCV eradication with DAA.

Criteria for Inclusion:

- **i)** Individuals aged 18-60 years.
- **ii)** Both males and females were considered.
- **iii)** Only Individuals with chronic HCV who had achieved an end of treatment response post 12 weeks of DAA administration.
- **iv)** Known type 2 Diabetes Mellitus cases who had pre-treatment HbA1c levels above 7.5 %.

Criteria of Exclusion:

- i) Individuals in the Child Pugh Class B and C.
- ii) Documented dual infection with HIV or hepatitis B virus.
- iii) Established liver cirrhosis or hepatocellular carcinoma.
- iv) Severe accompanying conditions like chronic obstructive pulmonary disease, end-stage renal failure, or congestive heart failure.
- v) Administration of drugs affecting glycemic balance e.g. steroids.
- vi) Documented allergy to DAAs or related medications.
- vii) Expecting mothers or those breastfeeding.
- viii) Those who are not willing or able to adhere to the study's protocols and follow up demands.

Upon acquiring clearance from GTTH ethics committee, a forward-looking cohort analysis was undertaken. Patients fulfilling the inclusion criteria were enrolled in the study after informed written consent.
Initial data of the participants, including age, gender, T2DM's duration, span of HCV infection and genotype were recorded. All HCV patients underwent DAA treatment with oral Sofosbuvir 400mg / velpatasvir 100mg combination daily for a three-month time period. Pre-treatment, blood samples included HbA1c, Fasting Blood Glucose level, random blood glucose, Liver eenzymees measurements including Alanine Aminotransferase, Aspartate Aminotransferase, Serum Bilirubin, Albumin and prothrombin time. The Abbott M-2000 system, was used for real-time PCR HCV RNA plasma levels determination with its sensitivity threshold of 12 IU/mL.

After 12-week duration of therapy, HCV-RNA PCR test was repeated to determine viral load, aiming for ETR readings below 12 IU/L after DAA administration. Metabolic profile including HBAIC, FBS and RBS were also repeated. Data examination was carried out utilizing the Statistical Package for Social Sciences (SPSS), version 24. To evaluate the primary attributes of the study's participants, descriptive statistics were employed. Continuous data points were represented either as mean ± standard deviation (SD) or as median within the interquartile range, contingent upon the situation. Categories of data were denoted through their frequency and proportion. The study's primary focus was on alternations in HbA1c levels from the initial measurement to 12 weeks post-finalization of DAA treatment. Any difference in HbA1c values from the start to 12 weeks post-treatment was evaluated via the paired t-test or the Wilcoxon signed-rank test. Alterations in FPG and RBG readings between the start and the 12-week mark were assessed through the paired t-test or the Wilcoxon signed-rank test. All the statistical evaluations were two-sided, with a p-value less than 0.05 was considered to be of statistical significance.

Results

In this study of 100 patients, 71% (n=71) were female and 29.0% (n=29) were male.

Regarding age distribution, 32 of the participants were between 24 and 36 years old, 48 were in the 37-48 years bracket, and 20 were aged between 49 and 60 years.
Mean age of study participants was 46.5 ± 7.34 years.
When examining the duration of diabetes, 28 had been diabetic for 1-3 years, 40 were diabetic for 7 years, and 32 had a diabetes history of 8 years or more. Duration of HCV infection, 34 had been infected for 1-3 years, 46 for 4-7 years, 10 for 8-10 years, and 10 had infection for more than 10 years. The average duration of their diabetes was reported as 8.2 ± 3.20 years, while the HCV infection persisted for an average duration of 6.4 ± 5.40 years. Baseline HbA1c was 9.70 ± 1.60, fasting blood sugar averaged 164.48 ± 36.50 mg/dL, and the mean random blood sugar was 288.30 ± 60.30 mg/dL. When evaluating Liver Function tests mean serum bilirubin was 1.14 ± 0.41 mg/dL and a serum albumin level of 3.50 ± 0.68 g/dL. Amongst Liver enzymes ALT had mean value of 56.69 ± 4.80 IU/L, ALP averaged at 120.44 ± 56.30 IU/L, and the mean PT duration was 11.40 ± 1.28 seconds. (Table 1)

Table 1: Baseline Clinical and Laboratory Parameters

Parameter	Mean	Std.Deviation
Age	46.50	7.34
Duration of Diabetes	8.20	3.20
Duration of HCV infection	6.40	5.40
ALT	56.6	4.80
ALP	120.4	56.30
PT	11.40	1.28
Serum Bilirubin	1.14	0.41
Serum Albumin	3.13	0.78
Basline_HbA1C	8.80	1.60
Baseline Fasting Blood Sugar	164.48	36.50
Baseline Random Blood Sugar	288.30	60.30

In our study, after three months of treatment, the fasting blood sugar in patients averaged at 116.68 ± 26.86 mg/dL. Their random blood sugar post-three months of HCV treatment was 190.70 ± 40.24 mg/dL. Additionally, the HbA1c levels after the same duration were recorded at 7.70 ± 1.58%.
In our study, mean difference in fasting blood sugar (FBS) from baseline to ETR was found to be a decrease of 48.70 ± 22.20 mg/dL (p Value<0.05). Similarly, the mean difference RBS over the same duration showed a reduction of 98.00 ± 39.70 mg/dL (p value <0.05). Quite interestingly, HbA1c levels also showed a decline of mean difference of 1.10 ± 0.82% from baseline to the three months mark (p value<0.05).

Table 2: Difference in Glycemic Parameters from Baseline to ETR

Parameter	Mean	Std. Deviation	P Value
FBS: Mean difference from baseline to 3 months	48.70	22.20	<0.05
RBS: Mean difference from baseline to 3 months	98.00	39.70	<0.05
HBAIC: Mean difference form baseline to 3 months	1.10	0.82	<0.05

In our study cohort, the ETR with SOF VELPA combo showed a remarkable sero-conversion of Hepatitis C infection, with 100% of patient getting negative PCR results at the end of treatment. So, all the study participants were given follow ups and regular monitoring done to sustain the compliance.

Discussion

Hepatitis C Virus infection is a global health concern, that has been silently

spreading world-wide. WHO has estimated that it affects 170 million people, or 1-2% of the global population[1]. Developing countries, like Pakistan, is also hit by this infection at an alarming rate, with data suggesting that 6.8% of Pakistan's adult population has HCV infection[2]. Once HCV infection is not properly taken care of, it then leads to a lot of host liver-related complications, ranging from the implication of effects of cirrhosis to the fatal complications like hepatocellular carcinoma[3]. HCV is further subdivided into six major genotypes and several serotypes. Predominant genotype of HCV in Pakistan is Genotype 3, which is claimed to be easy to treat[4]. But the actual issue is the suggested interplay between HCV and Type 2 Diabetes Mellitus. It has been seen that around 70% of individuals with chronic HCV infection stand have an increased risk of developing type 2 DM[5]. This is because of alterations in insulin resistance and glucose metabolism by various mechanisms attributed to HCV. Although the pathways of this connection are not clear, but what we do recognize that HCV induces proteins which do affect insulin receptors thus raising inflammatory cytokine levels. This leads to increased insulin resistance and ultimately T2DM[17]. The development of T2DM or worsening of already present T2DM can be attributed to fundamental disturbance of insulin resistance, thus tissues such as the muscle, liver and adipose becoming less responsive to insulin[6]. This leads to a pressure on the insulin-producing beta cells of pancreas to produce more and more insulin, thus gradually losing their ability to produce sufficient amounts of insulin, a state called burned out or stressed beta cells. Although, genetic predispositions play a role in its onset, environmental and lifestyle factors, especially poor diet, lack of physical activity, and resultant obesity, have their own role in disease development[7].

In recent years, the number of Pakistani populations with diabetes is also on the rise. In 2016, 11.77% of the population had diabetes. This value increased to 16.98% in 2018 and further escalated to 17.1% in 2019. Now, international diabetes federation has reported that a concerning 26.7% of Pakistani adults had diabetes in 2022, which makes it approximately 33 million people[18]. Of particular concern is the situation in which a patient is having both T2DM and HCV infection. In a study published on the prevalence T2DM among HCV infected patients from Khyber Pakhtunkhwa (KPK), it was found that 26.42% of T2DM in patients are concomitantly infected with HCV[10]. In another local investigation, a significant correlation was observed between HCV infection and the incidence of T2DM. It reported a DM prevalence of 34.80% in HCV infected individuals. Interestingly, the male patients exhibited a higher DM prevalence of 40.4% compared to females who showed a prevalence rate of 31.20%[11]. Conditions like metabolic syndrome, dyslipidaemia, central adiposity or hypertension can also increase the risk of T2DM if present alongside. These metabolic derangements might create a synergistic effect, thus markedly elevating diabetes risk[9].

Treatment of chronic HCV has seen substantial advancements in the recent past. From the era of interferon and ribavirin usage to now new medications known as direct-acting antivirals (DAAs). These antiviral agents offer higher cure rates, which in turn leads to better sustained virologic response (SVR) rates and hence, eradication of the virus from the body. They also offer fewer side effects than previous therapeutic regimens[12]. This achievement prompted researchers to probe its impact on metabolic derangement improvement. A study by Eslam et al. in 2011 gave the first indications of a positive relationship between HCV eradication and improvement in insulin sensitivity. In his work, patients who secured an SVR following DAA treatment experienced a

drop in their HOMA-IR levels, as compared to those who didn't[14]. This highlighted the metabolic benefits of achieving SVR but also provided an incentive to prioritize HCV eradication in those who need metabolic improvement as well.

On the same lines, we also aimed to investigate the potential of DAA therapy on achieving HBA1C after achieving HCV eradication. The core hypothesis of this study is that achieving eradication of HCV can pave the way for better glycemic control among co-diagnosed patients of HCV and type 2 DM. HCV infection alters the body's immune response, leading to an increased secretion of pro-inflammatory cytokines, particularly TNF-α and IL-6. These cytokines reduce the insulin signaling thus leading to insulin resistance. Upon HCV eradication, the levels of these cytokines drops leading to an enhanced insulin sensitivity[15 16]. In our study, a total of 100 type 2 DM patients with chronic HCV infection were given Sofosbuvir and Velpatasvir as a dual therapy for three months. They were then evaluated for HBA1C drop pre- and post- treatment. Luckily due to good follow ups and advice, 100% patients achieved SVR. The mean drop of HBAIC observed in our study was 1.10 ($p<0.05$). This result is in complete agreement to work which has been done previously by Yuan et al. They reported a significant glycemic improvement after receiving DAAs therapy; in the form of > 1% reduction in HbA1c level (p value < 0.001). Moreover, their large group of study patients demonstrated reductions in FPG levels, whereas the group that did not achieve SVR showed no significant change in FPG levels. The difference was statistically significant for the SVR group ($p <0.001$). While it was non-significant for the non-SVR group ($p=0.267$)[19]. In another work done by Boraic et al., 240 chronic HCV patients were analyzed for the effects of DAA therapy on glycemic indices. Upon achieving SVR, the diabetic subset showed a decline in HbA1c levels from an initial 7.6 ± 0.69 to 6.7 ± 0.78, while the non-diabetic group showed a reduction from 5.8 ± 0.5 to 5.1 ± 0.3. This study further showed a significant drop in uncontrolled T2 DM cases from 22.4% pre-treatment to 5.2% post-treatment[20]. This is also in close agreement to our study. In an analysis by Zied et al. Comparative assessments of glycemic parameters before and after DAA treatment showed almost similar results to our study. In their study, FBS prior to treatment averaged 219.06 ± 111.36 mg/dl, which decreased post-treatment to 112.37 ± 20.66 mg/dl, ($p=0.009$). RBS initial levels were 309.78 ± 108.7 mg/dl, which subsequently reduced to 191.2 ± 55.15 mg/dl after treatment ($p=0.001$). HbA1c percentages also showed drop of >1 ($p <0.05$)[21]. These results of his work are also in close agreement to results of our study.

A similar work done by Akhtar et al., showed that patients who were having high baseline HbA1c and achieved SVR, had better HbA1c reduction post-treatment compared to non-achievers[8]. Similarly, Hum et al. reported that patients with a higher drop of 0.98 % HbA1c was seen in those who achieved SVR[22]. Our observations closely align with past research, reinforcing the validly and reliability of the results. Although in all these studies different antiviral regimens were used and for different time periods as well still removal of virus from body led to improvement of metabolic profile. However, there were some limitations to our study. The absence of a control group, untreated for Hepatitis C but monitored for glycemic parameters, may have clarified biasness. Also relying on patients to self-report their compliance to therapy usually raises questions of accurate data. Additionally, our study monitored patients for ETR response but longer-term impacts on glycemic parameters must also be seen for sustainability of results. Future studies should look for a more extended period of monitoring, to understand the long-term implications of DAA therapy on glycemic control.

Conclusion

Hepatitis C Virus affects the metabolic profile of patients by increasing the insulin resistance, due to which there is worsening of Glycemic control of T2DM patients. Once eradication of HCV is achieved HBA1C is reduced by almost a value of 1 in T2DM patients co-infected with Genotype 3 HCV infection.

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Author's Contribution:

TT: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
AW, MRJ, UK, UH: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

PAKISTAN JOURNAL OF GASTROENTEROLOGY

Original Article

Incidence of obesity and overweight status amongst Type 2 Diabetic patients visiting a tertiary referral hospital of Lahore

Taha Tariq, Muhammad Ali, Asia Mehmood, Mohammad Rohaan Ajmal, Azan Ali, Usman Akram, Iman Ijaz, Maryam Faseeh, Seemab Shahid, Umer Hayat

Department of Medicine
Ghurki Trust Teaching Hospital / Lahore Medical & Dental College Lahore.

ABSTRACT

Objective: Diabetes continues to be one of the most prevalent global and local health problems as per IDF data. A strong relationship between obesity, overweight, and diabetes has been established and thus requires a better understanding of the prevalence of obesity and overweight among type 2 diabetics for their better management and prevention of complications. This study evaluates the incidence of overweight and Obesity amongst Type 2 diabetes patients visiting the OPD clinic of Ghurki Trust Teaching Hospital Lahore.

Method: The study sample comprised 500 type 2 diabetics who attended the diabetes clinic at GTTH, a tertiary care hospital in Lahore. All the confirmed type 2 diabetes cases were included in the study sample. The patients who had undergone any gastric surgery for weight loss or were taking weight loss medication were excluded. Data was analyzed using SPSS Statistics version 24.

Result: The BMI was measured in 500 patients (293 males and 207 females) who attended the clinic. According to the measured BMI, 113 (22.6%) were non-obese i.e. BMI 18.5-24.9(M=70(23.9%) and F=43(20.7%). Overweight (BMI 25-29.9 kg/m^2), and obese (BMI$\geq$ 30kg/m^2), were 224(44.8%) and 126 (25.27%) respectively. Female were more overweight than males (40.9% vs 50.2%) and also grade II obesity was more in female than male T2DM patients (6.4% vs 14.9%)

Conclusion: The prevalence of obesity in patients with type 2 diabetes mellitus in our population is high, especially in females.

Keywords: Obesity, Overweight, Type 2 Diabetes mellitus, HbA1c, BMI

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Corresponding Author: Taha Tariq **Email: tahatariq2201219@gmail.com**
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Introduction

Diabetes is an international concern; it knows no borders and does not discriminate among social classes[1]. Prevalence of Diabetes, especially T2DM, is expected to increase significantly with time, thus, further adding to the financial burden on healthcare budgets globally[2]. Early detection of the disease and associated comorbidities can significantly help in reducing the economic burden but also decreasing the associated mortalities and complications like cardiovascular comorbidities, blindness, limb amputation, and renal failure[3]. Unluckily, the prevalence of diabetes mellitus continues to increase globally as well as in Pakistan. Around 573 million adults have DM worldwide, out of which 32 million people are in Pakistan[4]. Due to this high prevalence, Pakistan, at the moment, ranks third in the world in terms of prevalence of diabetes[5].

On the other hand, obesity has also become a global pandemic with 1.9 billion people being overweight and 630 million people obese as per 2024 data[6]. Both these diseases lead to increasing diabetes and CVD related mortalities. At least 2.8 million mortalities worldwide are attributed to obesity every year[7]. Pakistan is no different in terms of obesity from the rest of the world, currently ranking tenth with a prevalence of overweight adults being 22.8% and that of obesity at 5.1%[8]. According to published literature, patients having greater BMI are at higher risk of having diabetes mellitus and its complications9, and vice versa. Those who are overweight or obese have seven and three times more risk of developing DM respectively. And, those who are diabetic and then they put on

weight become more insulin resistant, thus need more medicines and more complications arise from the disease. According to local data and work done in the South Asian region, the incidence of obesity and overweight is quite variable, with a range of 45-90 % in various studies[10] [11].

In this study, we have attempted to find out the incidence of overweight and obesity in Type 2 DM patients visiting the outpatient clinic of a tertiary care hospital, which may reflect true value in our region and plan treatments and management accordingly. This may help in reducing complications and decreasing associated morbidity and mortality.

Materials and Methods

500 patients with confirmed type 2 DM who attended the diabetes clinic between October 2023 and October 2024 were enrolled in the study after informed consent. Patients having type 1 DM, patients who could not stand, i.e., are wheelchair bound, pregnant women, patients who were taking any therapy for weight loss, or had undergone any Bariatric procedure were excluded from the study.

Weight and height of each subject were measured and recoded. Weight was measured in kg (to the nearest 0.5kg) using a calibrated scale, on a firm horizontal surface, without shoes and with the subject in light clothing. Height was measured (in metres) to the nearest 0.1cm. BMI was calculated by dividing the weight (kg) by the square of the height in metres (m^2). Body mass index (BMI) – was expressed in kg/m^2. Subjects with BMI <18.5 were classified as underweight and those having BMI of 18.5–22.9 were grouped as normal weight. Those with BMI of 23.0–24.9 were overweight and those with ≥25.0 were classified as obese. Obesity was further subdivided into grade I (BMI=25.0 −29.9), grade II (BMI≥30), respectively.

Continuous variables were evaluated by descriptive statistics, using means and standard deviation (SD), and differences measured by t-test. Confidence intervals (95% CI) were calculated for precision of sample estimation, variability of the

characteristics, and degree of confidence being studied. Median values and interquartile range (IQR 25-75%) were also used to show the central tendency. Categorical variables were expressed as numbers and percentages and their difference was evaluated by the chi-square test. Spearman test was used for correlation for ordinally constructed variables, and its p-value. All statistical analyses were two-sided, using 5% significance level, i.e. significance was defined as p value < 0.05. Analysis was performed using SPSS software, version 24.0 for Windows (SPSS Inc, Chicago, Illinois, USA). Written informed consent was taken from all participants and the study was conducted per the Declaration of Helsinki. The ethics committee of GTTH also approved the study.

Results

500 patients were included for this study, 293(58.6%) were male, while 207(41.4%) were females. The median age of the participants was 53.0 years with a range of 28–72 years. Male gender was older with a median age of 54.0 years compared with a median age of 51.0 years for the women (p=0.94). The mean duration of DM was 6.2 years and was longer among men compared with women, i.e. 7.2 years vs 5.2 years, p=0.04. Table 1

Table 1. Gender distribution and BMI stratification

Age Range	Male			Female		
Years	No	BMI Mean ± SD	S.E	No	BMI Mean ± SD	S.E
Over all	293	27.4 ± 3.2	0.44	207	28.2 ± 2.4	0.34
25-34	43	24.2 ± 1.6	0.34	17	24.6 ± 2.6	0.37
35-44	80	25.6 ± 2.2	0.33	42	26.2 ± 2.4	0.42
45-54	122	25.4 ± 3.2	0.63	108	26.8 ± 3.2	0.6
55-64	32	26.2 ± 2.8	0.40	33	26.4 ± 2.8	0.42
65	16	25.8 ± 2.6	0.20	7	26.2 ± 2.6	0.36

Table 1 shows the BMI values of the study participants. The incidence of obesity among the study participants was 25.27% and was higher among men compared with women (27.3% vs 25.2% p=0.18), but the difference was not statistically significant. Overall incidence of overweight was 44.8 % with females being more overweight than males (50.2% vs 40.9%) p value <0.001.

Table 2. BMI values of study participants according to WHO criteria for Asian population

BMI Category	MI Value	Male % n=293	Female % n=207	Total n=500
Under weight	< 18.5	23 (7.84%)	10 (4.83%)	23 (4.6%)
Normal	18.5 - 22.9	70 (23.89%)	43 (20.77%)	113 (22.6%)
Over weight	23.0 - 24.9	120 (40.95%)	104 (50.24%)	224 (44.8%)
Obese	≥ 25	80 (27.30%)	50 (24.15%)	126 (25.27%)
Grade I	25-29.9	51 (17.40%)	13 (6.28%)	63 (12.6%)
Grade II	>30	29 (9.89%)	37 (17.86%)	63 (12.6%)

Table 2 shows the number of the participants based on various BMI categories.

There was a significant difference between the mean BMI for both genders in various age groups. The peak difference in the mean BMI between females and males was in those aged 45-54. In patients with a low or normal BMI, there was a male preponderance. Among the group with a BMI < 18.5, there were 23 (7.8%) males out of 293 and 10 (4.8%) out of 207 were females (P = 0.008). Among those with normal weight (BMI, 18.5-22.9 kg/m^2), there were 70 (23.8%) out of 293 males and 43 (20.7%) out of 207 females (P < 0.0001). In the overweight group (BMI of 23-24.9 kg/m^2), 120 (40.9%) were male and 104 (50.2%) were female (P <0.001). In the group with mild obesity class 1 (BMI of 25-29.9 kg/m^2), there were 17.4% males and 6.28% were females, P < 0.0001. In the group with moderate obesity or class 2

(BMI ≥ 30), we found a much higher rate of obesity among the females than males with the incidence of 17.86 % vs 9.89 % in males ($p < 0.0001$).
Majority of our patients, 52% were on combination therapy with Metformin and Glibenclamide, 28% of patients were either on sulphonylurias with SGLT2 inhibitor, while 20% of patients were on a combination of insulin with Metformin. All patients were on one of these regimens.

Discussion

Obesity is one of the modifiable risk factors for type 2 DM. It has been linked to various complications including elevated blood pressure, cardiovascular disease, lipid disorders, Diabetes Mellitus, osteoarthritis, sleep apnea and related conditions[12]. In individuals with obesity, there is impairment of glucose-dependent insulin secretion leading to increased gluconeogenesis and hence worsening/ development of DM. The risk of type 2 DM also increases exponentially with an increase of BMI[13].

In our country DM is on the rise and every fourth adult is suffering from it[5]. Similarly, Obesity is more prevalent in Type 2 DM[7]. We conducted this study to find out the incidence of Obesity in the adult population visiting the GTTH Diabetic clinic. In our study, the overall mean BMI for females was 28.2 ± 2.4, while for males was 27.4± 3.2. Our results show that overweight patients were the most common entity, with around 45 % of diabetic patients being overweight, and amongst those 45 %, the majority were females. In contrast, around 25 % of the total screened people were obese, with the majority of them being males. Interestingly, Grade I and Grade III obese were predominantly males, while Grade II obese were males. We have used BMI as a marker to differentiate between the overweight and obese population. Same criteria have been used by various previous studies done on the same topic.

The prevalence of overweight and obesity amongst T2DM patients in this study was markedly higher than the value in the general population, but these values are consistent with studies and data coming from other settings, which showed similar or higher values in T2DM patients[8 9 10]. When we scrutinize the data, it is revealed that high prevalence has been reported in countries which are labelled as higher income countries[21]. In UK, approximately 86%–90% of T2DM patients had BMI≥25 [14] in Australian studies, 53% were in obese category and 32.8% were in overweight;[15] in a Saudi Arabian study, 87.5% had BMI ≥25 with prevalence found higher in females (87.7%) than in males (83.1%)[16]. African data shows varying rates of obesity in Tanzania (85.0%),[17] Sudan (64.4%),[18] Ethiopia (40%),[19] Nigeria (27.4%–83%) [20]. Urbanisation, globalisation, adoption of processed food eating habits, and indeed reduction of physical activity all contribute towards the increasing trend of overweight and obesity.

In our study, the incidence of overweight (BMI ≥ 30 kg/m^2) was more in women as compared to males. Many factors have been associated with an increased risk of obesity and DM in females, which may be dietary habits and more sedentary lifestyles as compared to males. In a remarkable study done in Saudi Arabia[22], working women had a lower rate of obesity and overweight than non-working ones, which clearly goes in favor of the lifestyle of females and refraining from exercise, which leads to more weight gain. Same might be the reason for increased incidence of females being grade II obese as compared to males. Literature shows that obesity has increased in the general population and T2DM as well in Asian countries[23] and simultaneously the risk of diabetes mellitus in the Asian countries is raised even at lower BMIs as compared to countries from other continents. A study conducted in Pakistan revealed that 72 % of TDM2 patients had obesity, and most of the obese patients were

females[24]. This value is far less than the value in our study. Our patients were coming from a more affluent and educated class, which may be the reason for this. In another study in the local population, 89.9% of the studied population was overweight and obese, and many were diabetic too[25]. This frequency of high obesity in other studies than our study may also be due to regional demographics and lifestyle variations, and it may be the reason for such a wide variation.

There are certain strengths and limitations in our study. We have used a simple parameter of BMI as a benchmark of obesity and overweight, and a small sample size was used, which cannot reflect the overall incidence of the country, but can act as a source of further research and data collection. Our study was conducted in the outpatient diabetes clinic in a private health facility and did not include patients visiting public health facilities so the results may not apply to the general population. This data was not designed for any research purpose, wasn't validated, and had no quality checks done for plausibility and completeness, and only a very limited number of variables were captured. Waist circumference and waist to hip ratio may also have been used to further strengthen the results.

Conclusion

Overweight and obesity were high among T2DM patients of our study population and may contribute significantly to the morbidity and mortality of T2DM. Despite being of high value, our results of obesity are less than the values in other local studies. More knowledge and access to healthcare professionals through media and availability of healthcare professionals may be the reason. Still then, appropriate strategies to improve nutrition and promote weight loss in TDM2 are urgently needed to combat this increasing health challenge.

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Author's Contribution:

TT: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
MA, AM, MRJ, AA, UK, II, MF, SS, UH: Collected the data, critical review and preparation of manuscript.
All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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Original Article

Serum Alpha Fetoprotein as a Predictor of Tumor Size in Hepatocellular Carcinoma

Muhammad Abdullah[1], Aman Nawaz khan[1], Ummara Siddique Umer[2], Muhammad Kamran Khan[1], Ghulam Syed Ghaus[2]

1.Interventional Radiology, Rehman Medical Institute, Peshawar.
2. Diagnostic Radiology, Rehman Medical Institute, Peshawar

ABSTRACT:

Objective: To evaluate the relationship between serum alpha fetoprotein (AFP) levels and tumor burden in hepatocellular carcinoma (HCC) patients.

Methods: This cross-sectional analytical study was conducted in the Interventional Radiology Department of Rehman Medical Institute from May 2016 to November 2022. Patients with chronic liver disease and concurrent HCC were included, while patients with liver metastases from other primary malignancies were excluded. Demographic characteristics, clinical information, laboratory investigations, and imaging modalities were considered. Patients were classified according to AFP levels and tumor diameter. Descriptive statistics (frequencies and percentages) and inferential statistics using Spearman's rank-order correlation test were employed. In addition, sensitivity and specificity of AFP levels for predicting larger tumor sizes were calculated.

Results: A direct positive association was observed between AFP levels and tumor size (Pearson Chi-Square = 220.091, $p < 0.001$). Most patients with AFP levels >2000 IU/mL had tumors >5 cm in diameter (n = 127). Using an AFP cutoff of >400 IU/mL to predict tumors >5 cm, sensitivity was calculated as 62.0% and specificity as 42.8%. With a higher cutoff of >2000 IU/mL, the sensitivity was 27.0% and specificity 34.4%. In addition, patients with higher AFP levels had significantly larger tumors, more frequent vascular invasion, and extrahepatic metastases. Histopathological confirmation (performed in a subset of cases via ultrasound-guided biopsy) supported the imaging diagnosis of HCC.

Conclusion: Elevated serum AFP levels are positively associated with larger tumor size and advanced tumor progression in HCC patients. Although AFP is a useful biomarker for estimating tumor load, its sensitivity is limited, particularly when used alone. Therefore, AFP should be interpreted in conjunction with imaging studies and, where applicable, histopathological confirmation to improve diagnostic accuracy.

Keywords: Hepatocellular carcinoma, Alpha fetoprotein, Tumor size, Sensitivity, Specificity

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Corresponding Author: Muhammad Abdullah **Email:** abdullahkmcite@gmail.com

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide and ranks as the sixth most frequently diagnosed cancer and the third leading cause of cancer-related death. Approximately 790,000 new HCC cases are diagnosed annually, with more than 700,000 deaths per year, particularly in regions with high hepatitis B and C virus prevalence. As the incidence of HCC increases, there is a growing need for efficient diagnostic and therapeutic strategies. Biomarkers such as AFP play an important role in assessing disease progression, predicting prognosis, and monitoring treatment response. AFP is a glycoprotein synthesized during fetal haematogenesis and normally declines postnatally. However, in adults, elevated AFP levels are primarily associated with liver diseases such as HCC, making it a valuable diagnostic tool.

Nevertheless, AFP has several limitations. Its levels may be elevated in nonmalignant conditions, including liver regeneration in chronic liver disease, which can lead to misdiagnosis. Therefore, understanding the correlation between AFP levels and tumor characteristics—including size—is essential to improve diagnostic accuracy and patient management. Previous studies have produced inconclusive results regarding the strength of this relationship, necessitating further research to clarify the role of AFP in predicting tumor burden in HCC.

Materials and Methods

This cross-sectional analytical study was carried out at Interventional Radiology Department of Rehman Medical Institute, Peshawar, over the period from May 2016 to Nov 2022. In the study, patients with chronic liver disease and diagnosed cases of Hepatocellular Carcinoma were enrolled. In this regard, patients with primary liver lesion other than HCC and metastasis were excluded. Demographic details like age, gender, and place of residence were also included as preliminarily structured templates involving general history and physical examination were taken.

They were followed by routine hematological and biochemical parameters, the amount of total protein, albumin/globulin ratio, serum albumin concentration and blood serum antigen of HBsAg, antibody of anti-HCV and AFP. Most of the patients were diagnosed having typica features of HCC with supporting findings, rest were having ultrasound guided biopsy. Patients were grouped based on their serum AFP levels into three categories: Group I, AFP less than 20 IU/ml, considered as the normal range; Group II, moderate increase in AFP, in the range of 20-399 IU/ml; Group III, AFP greater than 400 IU/ml referred to as highly raised. Similarly, patients were classified based on tumor size: This is the rationale for classifying patients into three groups: Group A with tumor size of <3 cm, Group B with tumor size of between 3-5 cm, and Group C with tumor size of >5 cm.

Moreover, Spearman's rank correlation test was used to assess the corresponding relationship between serum AFP levels and tumour size, with an assigned significance level of r = 0. 01. Descriptive statistics analysis was carried out in this study by using Statistical Package for Social Science (SPSS)

software version 27 to achieve high accuracy in the findings. This approach was designed to assess the correlation of serum AFP levels with tumor size of HCC patients and possibly offer some practical suggestions.

Results

The study included a total of 882 patients, with a mean age of 57.69 years (SD = 12.057). The gender distribution was 69.2% male (n = 610) and 30.8% female (n = 272). Among the patients, 80.2% (n = 707) were diagnosed with hepatocellular carcinoma (HCC), while 19.8% (n = 175) had other diagnoses. Treatment details indicated that 21% (n = 185) received complete treatment (CT), 54.2% (n = 478) received partial treatment (PT), and 24.8% (n = 219) received no treatment (No TX) for viral hepatitis B or C.

Table 1: Demographic and Clinical Characteristics of the Study Population

Statistic	Value
Mean Age (years)	57.69
Standard Deviation	12.057
Gender (Male)	69.2%
Gender (Female)	30.8%
HCC Diagnosis	80.2%
Non-HCC Diagnosis	19.8%
Complete Treatment (CT)	21.0%
Partial Treatment (PT)	54.2%
No Treatment (No TX)	24.8%

Table 2 presents the tumor sizes stratified by AFP levels. A statistically considerable relationship between AFP levels and tumor size was determined (95%confidence, chi-square = 99. 407, p < 0. 001). For the purpose of analysis, the patients were categorized based on the tumor size and AFP levels: The majority the patients with AFP levels >2000 IU/ml had tumors >5 cm (n = 127).

Table 2: AFP Levels and Tumor Size Cross-Tabulation

AFP Levels (IU/ml)	Tumor Size <3 cm	Tumor Size 3-5 cm	Tumor Size >5 cm	Total
<10	26	33	83	142
11-20	18	6	27	51
21-40	16	15	24	55
41-100	7	13	45	65
101-400	3	19	77	99
401-2000	7	17	88	112
>2000	4	8	127	139
Total	81	111	471	663

Pearson Chi-Square = 220. 091 whereby p < 0. 001, a high level of significance was also determined between AFP levels and HCC. Among the patients with elevated AFP levels, 155 patients with AFP >2000 IU/ml were diagnosed as having HCC.

Table 3: AFP Levels and HCC Diagnosis Cross-Tabulation

AFP Levels (IU/ml)	HCC	No HCC	Total
<10	145	137	282
11-20	51	9	60
21-40	52	9	61
41-100	67	5	72
101-400	102	8	110
401-2000	119	1	120
>2000	155	5	160
Total	691	173	865

AFP levels were also found to have positive correlations with two other parameters, namely; vascular invasion (VI) and extra hepatic disease (EHD). Hence, rates of VI and EHD were found to be significantly related to AFP levels; the higher the AF P level the higher would be the rates of VI and EHD.

Table 4: AFP Levels and Vascular Invasion (VI)

AFP Levels (IU/ml)	No (EHD)	Yes (EHD)	Total
<10	259	22	281
11-20	56	4	60
21-40	54	7	61
41-100	59	12	71
101-400	89	20	109
401-2000	82	36	118
>2000	113	45	158
Total	712	146	858

Table 5: AFP Levels and Vascular invasion (VI)

AFP Levels (IU/ml)	No VI	Yes VI	Total
<10	245	33	278
11-20	54	6	60
21-40	49	11	60
41-100	55	17	72
101-400	74	34	108
401-2000	60	57	117
>2000	55	102	157
Total	592	260	852

Sensitivity and Specificity Analysis

Using an AFP cutoff of >400 IU/mL (Group III), the combined number of patients was 350. Among these, 292 had tumors >5 cm. With the total number of patients with tumors >5 cm being 471, the sensitivity for detecting large tumors (>5 cm) at this cutoff is 292/471 (approximately 62.0%). Conversely, the number of patients with AFP ≤400 IU/mL was 313, among whom 134 had tumors <5 cm; thus, the specificity is 134/313 (approximately 42.8%).

For a higher cutoff (AFP >2000 IU/mL), 139 patients were positive, and 127 of these had tumors >5 cm, yielding a sensitivity of 127/471 (approximately 27.0%) and a specificity of 180/524 (approximately 34.4%).

The Spearman's rank correlation test shows: $r_s \approx 0.31$, $p < 0.001$. This result indicates a statistically significant moderate positive correlation between AFP levels and tumor size in HCC patients. In other words, as AFP levels increase, there is a tendency for tumor size to be larger.

Discussion

Our study confirms the beneficial association between serum alpha fetoprotein (AFP) concentrations and tumor size in HCC patients.

In the research by Munir et al. (2021) the mean age and gender distribution of HCC patients in Pakistan was comparable to ours. Munir et al. reported a mean age of 57.69 years similar to our study mean, but predominantly male.[6] This similarity in demographic distribution underscores our generalizability across populations and ethnicities.

In our study, the tumor size was larger in subjects with high AFP level. In fact, BMI, L-R, L / T ratios and prognostic nutritional index were high, platelets and AFP were high and most of the patients with AFP > 2000 IU / ml had tumors larger than 5 cm. This is consistent with the literature which mentions that increasing the size of the tumor increases the quantity of AFP created and released in the bloodstream. Thus this positive relationship (Pearson Chi-Square = 99. 407, p 0. 001) highlights the role of AFP in estimation of tumor load in HCC.

Anwar et.al (2020) also investigated the association between tumor size and AFP levels in relation to HCC tumor size.[7] Our study range of 101-400 ng / mL is in agreement with the positive correlation reported by Anwar et al. who also found significant correlations at AFP > 400 ng / mL.[7] In a similar study, Shaikh et.al (2016)

reported that patients with HCC with higher AFP levels had larger tumors and worse prognosis.[8] Their Chi-Square test results confirmed the statistical significance of the AFP-tumor size association and matched ours (2 = 99.407, df = 12, p 0.001).

Our results also showed that AFP levels were positively associated with HCC incidence. Among total patients with AFP > 2000 IU / ml majority were HCC patients (Pearson Chi-Square = 220). 091, p 0. 001). This finding confirms the general usefulness of AFP in the diagnosis of HCC, but also underscores the problem of specificity in that some elevated AFP positives were also not HCC. This requires the use of AFP in conjunction with other complementary techniques such as imaging and histopathology to limit false results.

Bai et al. reported that AFP greater than 200 ng / mL was associated with bigger tumor sizes and poorer prognosis; this is consistent with our finding that bigger tumors (> five cm) have been associated with high AFP (> 400 ng / mL).[9] This study confirms our results that tumors larger than 5 cm are strongly associated with AFP > 2000 ng / mL. Thus, very high AFP levels indicate the need for aggressive monitoring and possibly intensive treatment. Abbasi et al. also confirmed that AFP can detect HCC at levels above 400 ng / mL.[10] Our study supports this by demonstrating that elevated AFP levels are associated with advanced tumor stages. Their results further solidify AFP as a valid biomarker associated with tumor size.

Although AFP levels provide important information for diagnosis and prognosis, Toader et al. in 2019 and Laura et al. (2016) highlighted how important imaging methods such as MRIs and CT scans are for the identification and evaluation of HCC.[11,12] This supports our study's claim that AFP should not be the only diagnostic standard. Imaging studies need to be combined to characterize tumors.

Khan et al. (2022) supported our results by pointing out that AFP alone is not a reliable indicator of HCC.[13] Their research demonstrated that AFP measurements should be combined with imaging modalities to improve diagnostic precision and provide a comprehensive strategy for managing HCC.

The clinical implications of our study findings are multiple. With a Pearson Chi-Square value of 99.407 and a p-value 0.001, AFP levels are highly significant predictors of tumor size that clinicians can use to inform treatment decisions. Patients with AFP > 2000 ng / mL should be assigned to detailed imaging studies and closer follow-up as larger tumors are more likely to require intensive treatment.

In line with our conclusion that high AFP levels warrant aggressive medical intervention and close monitoring, Bajkani et.al (2019) found that elevated AFP levels are a prognostic factor in HCC.[14] This consistent finding demonstrates the role of AFP in treatment protocol development and diagnosis for improved patient outcomes.

Our study has some limitations despite the high correlation between AFP levels and tumor burden. First of all, as noted by Sahbbir et al. not all HCC patients have elevated AFP levels, suggesting that reliance on AFP alone may in some cases lead to underdiagnosis.[15] Hence, a combined strategy using imaging methods and AFP levels is recommended.

Furthermore, benign liver conditions can lead to elevated AFP levels, thereby complicating the differential diagnosis. This, as noted by Samant et al., necessitates interpretation of AFP results within the context of a larger clinical setting, where the importance of accurate diagnostic assessments for precise disease characterization was emphasized.[16]

Clinical Implications.

Furthermore, from the discovery of these biomarkers several clinical correlations can be inferred. First, they note that serum AFP is a good indicator of disease and tumor burden in HCC. Raised AFP levels may require more frequent monitoring and drastic management that may be beneficial to patients. However, this study also

highlights the disadvantages of applying AFP such as its nonspecific nature. In some instances, AFP might increase in chronic liver diseases like cirrhosis or hepatitis, complicating the diagnosis of HCC. Hence, AFP should be included in a combination of diagnostic methods based on imaging and biopsies to assess the disease status.

These results are consistent with earlier studies and also validate the impact of AFP levels and tumor size in HCC patients. Raised AFP values reflect larger tumor size, increased intravasation, and metastatic disease. Hence, AFP can be an objective marker of tumor mass and disease activity. Nevertheless, the results suggest low specificity of AFP and it must be utilized in conjunction with histopathology and imaging for correct diagnosis and treatment. Future work will require LWA of these observations and its replication in a multi-center large cohort of patients managed for HCC to improve the clinical value of AFP.

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Author's Contribution:

MA: Conceived and designed the study, involved in data collection, performed statistical analysis and writing the manuscript.
ANK, USU, MKK, GSG: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

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Original Article

Avoidance behavior as coping mechanism in patients with Irritable Bowel Syndrome

Saira Akhlaq[1], Nosheen Kazmi[1], Sajwal Hussain[1], Kalsoom Akhlaq[1], Ahmed Bajwa[1], Murtaza Kazmi[2], Shahzad Riyaz[2], Abdul Hadi[1], Muhammad Yaqoob Akhtar[1], Muhammad Rizwan[1]

1.Shifa Tameer-e-Millat University Islamabad, Pakistan
2. Shifa International Hospital Islamabad, Pakistan

ABSTRACT:

Introduction: Irritable Bowel Syndrome (IBS) and Somatization Symptoms Disorder (SSD) patients experience somatization symptoms that have a significant impact on their quality of life and their primary diagnoses as well. Coping strategies in these patients affect how they seek treatment and how they respond to different interventions. One of these coping strategies is "Avoidance behavior". The relationship between avoidance behavior in relation to demographic and social variables in IBS patients' needs to be better described.

Methods: This study was performed at Shifa International Hospital, Islamabad. Study participants aged 18 years and above who were seeking regular treatment in the respective units of Shifa International Hospital, were surveyed between March 1st 2023 and January 14th, 2024. Purposeful sampling was done to recruit study participants. Participants were eligible to participate if they had a diagnosis of IBS, or SD. Coping Strategy Indicator (CSI) was used to assess coping strategies in patients with IBS and SD.

Results: There was a total of 88 patients; 67 with IBS and 21 with SSD. With increasing age, the avoidance behavior decreased, with higher education levels avoidance behavior also increased.

Conclusion: Avoidance behavior was observed as a significant interventional target in IBS patients. This is most evident in the younger age group and those with higher level of education.

Keywords: Functional disability, Competence, Irritable bowel syndrome, Recurrent abdominal pain

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Corresponding Author: Saira Akhlaq **Email: saira.ssphe@stmu.edu.pk**

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Introduction

Coping is a potential psychological treatment target in irritable bowel syndrome (IBS)1. Negative effects of psychological factors as IBS can be minimized by decreasing catastrophizing and somatization.[2] Management if IBS and SSD requires as biopsychosocial approach to address the symptomology. Avoidance behavior is an important mediating variable when considering addressing quality of life in IBS patients in patients seeking treatment. Prevention or re-construction of avoidant behaviors in IBS treatment plan has been recommended as important interventional strategy to improve QoL in IBS patients. However, when reviewing the results, a difference has been demarked between avoidant behaviors and avoidant coping. The relationship of avoidant coping with Qol is insignificant yet the relationship of timeline as a pre-determinant of avoidant coping is significant in the mediation medel.[3] Similarly, when considering the role of avoidance behavior in the treatment with CBT of young adolescents with IBS, reduction in avoidance behavior and time are important mediating variables that affect GI symptomology in IBS adolescents.[4] When considering avoidance behavior as a treatment target, it has been observed that CBT is beneficial is reducing avoidance behavior due to decreased GI symptoms. However, the decrease in the magnitude of avoidance behavior does not result in the significant decrease in psychological distress. When considering GI symptoms versus psychosocial symptoms in IBS, CBT has a medium to large effect on GI symptoms severity. Whereas low-to-medium effect is observed with CBT for psychological symptoms severity in IBS patients.[5]

Despite being a functional disorder, it is unclear whether IBS symptoms occur because of somatic symptoms or whether the prevalence of IBS symptoms is co-incidental with somatic symptoms.[6] Avoidance behavior, personality disorders and demographic variables have been known to be associated with the presence of somatic disorders in clinical setting.[7] Moreover, illness perceptions appear to drive avoidant behavioral responses to IBS symptoms, which in turn predict reductions in quality of life. These relationships seem more pronounced among people who seek treatment for their symptoms.

Therefore, it has been stipulated that health care practitioners might help improve the quality of life in people with IBS by preventing or reconstructing avoidance begaviors.[3] This is best done through behavioral and psychological intervention such as cognitive behavioral therapy. Interestingly, however, differences have been observed between patients who reported early responses to CBT for changes in symptoms as compared to those patients who did not report early responses to CBT.[8] Similarly, effectiveness of CBT is a time-bound phenomenon as the effects of CBT are evident in IBS patients over a course of 6 months when used as a complementary intervention, yet these effects fade aways at 12 months.[9] These observations point towards as interplay of psycho-social factors that might predict which subgroup of IBS patients might best respond to targeted psycho-social interventions with regards to their coping strategies.

Understanding this relationship of demographic and psychological determinants of health with coping strategies will help tailor a cognitive behavioral approach, which is of essence in treating these patients.[6] This approach has the potential to facilitate the implementation of individual case-based protocols of treatment for GI symptoms in IBS patients. One such therapy is Acceptance and Commitment Therapy (ACT) that has the potential for better GI outcomes in patients with IBS,[10] provided the limited efficacy of CBT.[8,9]

Materials and Methods

An institutional review board (IRB) approval granted through the IRBs of Shifa Tameer-e-Millat University with an IRB#020-23. Research team members collected data by regularly following up with the patients after their clinical visits. The quantitative, prospective survey design was used to assess the trends of various coping strategies practiced by the targeted sample in response to differential disease diagnosis. The survey design included administration of two different types of questionnaires.

A purposeful sampling was done to recruit study participants. Participants were eligible to participant if they had a diagnosis of IBS, somatization, or IBS with somatization and were currently receiving treatment, with the assumption that study participants were using a certain type of coping strategy to address the burden of their illness, as avoidance coping holds due consideration in the treatment of physical symptoms for the respective diagnosis.
To increase recruitment without researcher bias, eligibility questions were used to define inclusion and exclusion criteria. Patients were screened for studies two screening question based on the eligibility criteria: "what is the type of your diagnosed? Patients who met the eligibility criteria, i.e., a diagnosis of IBS, IBS with somatization, or somatization were included in the study. Patients with a diagnosis of inflammatory bowel disease or psychological diagnosis other than somatization were excluded. G*Power was used to calculate a sample size of 55 study participants by using a moderate effect size (f=0.15) with alpha set at 0.05 and power at 0.80.11 A total of 100 participants completed the survey. Thus, the required sample size was met. Thus, study finding may be generalized to larger population.

Demographic variables were selected based on the literature review. Demographic data measurement included assessing age, gender, and education. We used the coping Strategy Indicator (CSI) instrument by James H. Amirkhan as the key tool in our study.[12] The reliability and validity of the CSI is greater as compared to the Ways of Coping Questionnaire (WOCP) that includes a construct of Escape avoidance by Lazarus and Folkman (1984).[13] Cronbach's alpha for the scales on the CSI range from .84 to .93, and yield stable scores i.e., test retest correlation averaging .82 across 4 to 8 weeks spans.[14] convergent validities have been demonstrated, both in terms of convergence with existing measures of coping, personality, and pathology, and in terms of no covariation with social desirability indices. Criterion validity of the CSI was predicted by its ability to predict actual coping responses that were observed in both laboratory simulation and real world settings. The items on the CSI denote three different coping strategies: problem solving, seeking social support, and avoidance.[16] Permission from the instrument's developer (Amirkhan) was obtained to use the CSI through an email. CSI questionaries were first scored manually in SPSS by calculating the total aggregate score for each construct within the questionnaire by adding up the raw scores for items within each construct. Scoring on the CSI questionnaire was done by following the instruction on the CSI scoring sheet. Each type of coping strategy denotes each construct on the instrument and there are 11 items under each construct. Each item is graded on a three-point Likert scale from 3-1 which means 11*3=33 is the maximum raw score possible on each construct. Whereas 8 is the minimum raw score possible for each construct.

Data was collected from the eligible participants after verbally obtaining informed consent. Verbal agreement to participate in the study. Survey data was recorded on reliable and validated

questionnaires either before or after their scheduled clinical visit. Some of the patients provided incomplete data and were therefore not included in the inferential analysis. Some of the patients refused to voluntarily participate in te study or some decided to withdraw from the study during the data collection process and were therefore excluded from the study.
Data accuracy was ensured by explaining each question to each study participants. All questionnaires had simple easy to read questions. The overall data collection process took about 11 months. Anonymity of the data collection process and data storage security was maintained. Statistical Package for social sciences (SPSS)17 used to secure an electronic database along with data analysis.

Results:

Descriptives for Study Samples

There were two different samples from two different populations for the stud. A total of 67 IBS patients and 21 SSD patients self-reported data. In the IBS sample, considering the age rangers: 28.4% were between 18-29 years old, 26.9% of participants were between 30-39 years, and 22.4% were 50 years and above. A large percentage of participants were males (59.7%) as compared to females (40.3%). Most participants had a high school diploma or equivalent degree (56.7%). In the SSD sample, majority of the participants were less than 50 years old (71.4%), and males (66.6%) as compared to females (33.3%). When considering education, high school diploma or the equivalent (61.9%) was the most common level of education, followed by higher than bachelor (28.6%) and higher than bachelor (9.5%).

To assess the test of normality, Kolmogorov-Smirnov test was performed. The results were significant which means that the assumption of normality was not met, yet the central line. Therefore, the distribution can be considered as a normal distribution, and parametric tests can be applied.

Coping Strategy Indicator (CSI)
The score for each item on the CSI scale were manually scored by following the developer's scoring guide to form continuous variables for calculating continuous scores.
Table.1

Table: 1 Mean CSI score by Constructs in IBS patients

Constructs	N	Mean	Std.Dev	Std.Error	Min	Max
Problem Solving	67	24.62	5.24	0.64	11	33
Seeking Social Support	67	21.74	7.56	0.92	11	33
Avoidance	67	21.85	4.96	0.61	13	31

CSI Scores by constructs (Somatization Disorder):

A mean score of 26.57(+/-5.24) was observed for problem solving. A mean score for 26.57 is in between the average mean score of 21.0 and 31.0 and equal to or greater than the mean score average which is 26 on the referent score. A mean score 19.48(+/-7.10) was observed for seeking social support coping. A mean score of 19.48 is in between the average mean score of 18.0 and 28.0 but below the mean score average which is 23 on the referent coping. A mean score of 23.29 is slightly above the average score range of 15.0 and 23.0 and above the mean score average which is 19 on the referent score. A problem solving mean score is equal to the general population. Whereas the mean score of seeking social support is lower than the general population, which reflects a negative outcome. Whereas a higher mean score for avoidance behavior a negative outcome.

Table 2. Mean CSI Scores by constructs in Somatization Disorder.

Constructs	N	Mean	Std.Dev	St. Error	Min	Max
Problem Solving	21	26.57	5.24	1.14	19	33
Seeking Social Support	21	19.48	7.10	1.55	11	33
Avoidance	21	23.29	5.56	1.21	14	32

Avoidance Behavior in Study Samples
Once sample t-test was conducted three times for three different samples. One-sample t-test was conducted on the study samples to assess of the means of samples for avoidance behavior are different form historic controls. A mean score for avoidance behavior on the CSI scale is 19. In the two samples, mean score for avoidance behavior in IBS patients and those with SD were statistically significant (<0.001).

Factors affecting Avoidance behavior in Somatization Disorder Patients

Age and Avoidance Behavior

Age significantly predicted variations in avoidance behavior as a coping strategy, $p<0.05$. R^2 for the overall model was 39.8%, a moderate effect size. The slope coefficient (B) of age was significantly differnet from zero in the model which mean that there was linear relationship of age with avoidance behavior. For each 1-point increase in age, coping scores for avoidance could be expected to decrease 2.3 point with increasing age, p=0.002, i.e, older adults were more than two times less likely to use avoidance behavior as a coping strategy than younger adults (see Table 3)

Table 3. Avoidance Behavior by Age in Somatization Patients

Model	Unstandardized B	COfficient St. Error	Standardized Coefficient B	T	Sig
1 Constant	**29.306**	**1.9954**		**14.996**	**<.001**
Age	**-2.385**	**.673**	**-.631**	**-3.544**	**.002**

Age, Education and Avoidance Behavior in IBS Patients

Multiple regression analysis was conducted to assess it variations in age and education predicted variation in the Avoidance Behavior scores (a mechanism that may be involved in the management of IBS). Age and education significantly predicted variations in avoidance behavior as a coping strategy, $p<0.05$. R^2 for the overall model was 14.2% a small to moderate effect size. The slope coefficient (B) of age and education were significantly different from zero in the model which means that there were linear relationships of age and education with avoidance behavior. For each1-point increase in age, coping scores for avoidance behavior decreased 1.2 points with increasing age, when adjusted for education. In the multiple regression model, the overall variation in avoidance scores by age decreased by 1 point when variation was calculated by adjustment for the variable of education. For each 1-point increase in education, coping scores for avoidance behavior increased 1.6 points, when adjusted for age. Thus, the magnitude of predicted variation in the outcome variable may be affected other variable in the model (see Table 4). In the regression model, the overall variation in avoidance scores by age decreased.

Table 4. Multiple Regression: Avoidance Behavior in IBS Patients by Age and Education

Model	Unstandardized B	COfficient St. Error	Standardized Coefficient B	T	Sig
2 Constant	22.295	1.687		13.218	<.001
IBS Age	-1.177	.449	-.304	-2.622	.001
IBS Edu	1.566	.741	.245	2.114	.038

a. Dependent variable: Avoidance Behavior in IBS patients

Discussion

Avoidance behavior may be considered as a psychological risk factor in persistent somatic symptoms and related syndromes and disorders.[18] Avoidance behavior holds special significance as a treatment target through cognitive behavioral therapy for improving GI symptoms in adolescent IBS patients.[4] Avoidance behavior is a type of maladaptive coping like catastrophizing that holds special significance in IBS symptom severity.[2] The role of avoidance behavior/coping is not new to symptoms treatment in IBS and SSD, especially when avoidance behavior has been linked with consequences like quality of life and avoidance coping with timelines;[3] and avoidance of potentially symptom-provoking situations, or the fear-avoidance concepts is not yet adequately addressed in somatoform disorders.[4]

Acceptance and commitment therapy (ACT) is an effective treatment for IBS symtoms[19] and psychosomatic symptoms.[20] acceptance is a phenomenon opposite to avoidance and based on the common-Sense Model of Self-Regulation (CSM) for the treatment of chronic illnesses.[21] Thus, avoidance behavior can only be decreased by increasing acceptance. Thus, it was needed to asses it the avoidance scores in our study participants are higher than the general population and if ACT would be the right choice that needs to be promoted for decreasing avoidance scores. Even though our study did not have implementation of ACT, as a first step we needed to identify if avoidance behavior was prevalent in our study participants. Thus, our study was first of its kind as it only measured avoidance scores in our context but also assessed avoidance scores by using a questionnaire[16] different than the avoidance coping strategy and quality of life.[3] The questionnaire that was used in our study has a referent score of 19 which means that the average avoidance score in the general population is 19 as was calculated by the developer after testing the reliability and the validity of the tool. Considering avoidance scores in our study samples of IBS patients and patients SD to be higher than the avoidance scores in the reference range, suggest a higher tendency for avoidance as a coping strategy in these two groups. Consequently, these points towards an increased need to address avoidance behavior as a treatment target in psychological intervention such as cognitive behavioral therapy (CBT) for improving symptomology.

An interesting finding in our study is that avoidance behavior decrease with increasing age. This finding can be synonymous with the fact that the study samples in our study included more younger patient as compared to older patents. This also corresponds with the increased significance of avoidance behavior in younger patients in a study that assessed the effectiveness of CBT in young IBS patients by targeting avoidance behavior as a treatment target for GI symptoms.[4] In short, age holds a special significance as a determinant of avoidance behavior in IBS patients as well as patients with somatization diagnosis, whether the relationship of age with avoidant behavior is assessed by considering avoidant behavior as mediating variable or as an dependent variable.

An exaggerated avoidance response as seen in our study emphasize the need to address avoidance behavior in patients with IBS and SD. This was especially noticeable for younger patients with lower educational background. Despite the role of avoidant behavior in treating GI symptomology in adolescent IBS patients, younger age was only an eligibility criterion in this randomized control trial.[4] In our study, demographic variable like age and education were assessed for the magnitude and the direction of their relationships with avoidance behavior. Younger age continues to be predictor variable for avoidance behavior in our study. This assessment

holds significance because even in a systematic review that was conducted to assess psychological determinants of persistent somatic symptoms, assessment of sociodemographic factors as risk factors was excluded.[17] Our current manuscript is a derivation from a larger grant-funded project and 50% of our study participants had a somatic symptom burden-cited in a study currently being submitted to another journal for publication. Therefore, socio-demographic variables in addition to psychological symptoms hold due consideration in IBS patients and somatization symptom disorder (SSD) patients. Despite the relevance of socio-demographic variables in relation to avoidance scores that are used a response strategy to symptomology in IBS patients and SSD patients, factors that contribute to expected increased avoidance scores in addition to sociodemographic variables may be explored. Multicentered assessments for consistency across larger populations, and a longitudinal study design for confirmability of findings over time may be conducted.

The current approach was taken to identify the modifiable factors associated with avoidance coping strategy. This approach is synonymous with a needs assessment approach-an approach to identify the gaps or the barriers to plan and implement corresponding interventions to minimize risk behaviors and promote protective behaviors. The current research is part of comprehensive planning process that will lead to subsequent interventions by integrating education about mechanisms that increase adherence to improved rates of effective coping and decreased rates of ineffective coping, especially when psychological interventions are needed to improve quality of life in IBS patients and SSD patietns.[14,21]

There is an unmet need not only at the local, national level but also at the global level that requires targeted approaches to manage symptoms in addition to the biomedical approaches for the selected samples. Thus, the study was conducted to understand the factors related to avoidance coping a key factor associated with symptom not only in IBS patients but also SSD patients.

Limitations and Recommendation

The study was based on the patient's enrollment from one tertiary care hospital despite intra-organizational collaboration. Therefore, in future multi-centered studies may be conducted to assess if the pattern prevails across different organization. Our study met the generalizability criteria for the IBS sample, yet the generalizability for SSD and IBS-SSD patients is not possible. In future, studies may be conducted to specifically enroll patients from the Psychiatry Department and patients with a primary diagnosis of IBS and a comorbidity of SSD. Furthermore, longitudinal study design may be planned to assess if the patients followed overtime still continue to use avoidance behavior especially in younger patients.

Conclusions

Avoidance behavior can be addressed by considering the role of sociodemographic factors in relation to avoidance behavior for addressing symptomology in patients with the diagnosis of either IBS or SSD; especially when socio-demographic variable like age and education act as causal factors influencing avoidance behavior in IBS patients: and increasing age alone as a causal factor that decreases the likelihood of avoidance behavior in SSD. Additionally, considering the role of ACT as an alternative to CBT for addressing avoidance behavior in IBS patients and SSD patients, our study is unique as it identifies the younger age group practicing avoidance behavior and needs ACT as a IBS patients and SSD patients.

Conflict of Interest

There is no conflict of interest involved.

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Authors Contribution:

SK: Conceived and designed the study, involved in data collection, performed statistical analysis and writing manuscript.
NK, SH, KA, AB, AH, MYA, MR: Collected the data, critical review and preparation of manuscript.

All authors have read, approved the final manuscript and are responsible for the integrity of the study.

Pakistan Journal of Gastroenterology

Pakistan journal of Gastroenterology, is being published by Pakistan Society of Gastroenterology since 1987. After a gap of few years, it is being relaunched with the same name but new format, additional focus and an augmented editorial board. International reviewers have been included to increase the impact of published material. we will continue to publish national and international articles in Gastroenterology, Hepatology, Endoscopy and metabolic disorders, and pledge to continue seamless articles publication without conflict of interest and any gaps in publication. We are striving to adopt new logistics and exploring new ways to develop and establish our journal.

We are still in brain storming phase of how to expand and create an identity in the galaxy of journals. We will be applying for indexation in HEC, PMDC, CPSP. Scopus, DOAJ and pubmed central and believe to achieve our goals in next two years' time.

We would like to have your feedback from content to cover art of present issue and impressive work coming our biannually.

Editorial Team
The Pakistan Journal of Gastroenterology

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Official Journal of Pakistan Society of Gastroenterology and GI Endoscopy