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Original Article

Hepatitis C virus associated ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, AFP, CEA, CA 125, CA 19-9, iPTH biomarkers, computed tomography and HCV burden of disease during pre COVID-19 era (2018-2019) and post COVID-19 era (2020-2022) in Pakistan

"ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, AFP, CEA, CA 125, CA 125, CA 19-9": biomarcadores iPTH associados ao vírus da hepatite C, tomografia computadorizada e carga de doença do VHC durante a era pré-COVID-19 (2018-2019) e era pós-COVID-19 (2020-2022) no Paquistão

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Abstract

The national burden of HCV has significantly mounted over the period of last few decades placing Pakistan at the worst placement of second largest burden of HCV globally. Herein for the first time from Pakistan, we examined clinical correlation of potential biomarkers with HCV. Nation-wide study was conducted on 13,348 suspected HCV patients during 2018-2022. During pre-COVID-19 era of 2018-2019, prevalence of HCV remained 30%. During 2018, among HCV positive patients, 91% of ALT, 63% of AST, 67% of GGT, 28% of Bili T, 62% of HB, 15% of HBA1C, 25% of CREAT, 15% of PT, 15% of aPTT and 64% of AFP were abnormal. During 2019, among HCV infected 74.47% of ALT, 63.54% of AST, 70.24% of GGT, 24.71% of Bili T, 8.77% of HB and 75% of AFP were raised. CT/CAT scan revealed 4.65% liver complications (mild 13.04%, moderate 30.43% and severe 56.52%). During 2020, HCV prevalence remained 25%. 65.17% of ALT, 64.20% of AST, 68.75% of GGT, 31.25% of Bili T, 20.97% of HB, 4.65% of CREAT and 73.68% of AFP levels were raised. CAT analysis revealed liver complications among 4.41% (14.81% mild, 40.74% moderate, and 44.44% sever). 85.71% of participants diabetes was out of control. During 2021, HCV prevalence remained 27.1%. ALT (73.86%), AST (50.6%), GGT (67.95%), Bili T (28.21%), HB (20%), CREAT (5.8%) and AFP (82.14%) levels were abnormal. During 2022, the levels of ALT (56.06%), AST (56.36%), GGT (56.6%), Bili T (19.23%), HB (43.48%), HBA1C (14.81), CREAT (18.92%), AFP (93.75%) were abnormal. CAT analysis revealed 7.46% liver complications (25% mild, 30.36% moderate, and 42.86% sever). During 2021-2022, 83.33% of subject's diabetes was not controlled.

Keywords: HCV, Pakistan, ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, tumor markers, AFP, CEA, CA 125, CA 19-9, iPTH.

Resumo

A carga nacional de HCV aumentou significativamente ao longo das últimas décadas, colocando o Paquistão na pior colocação da segunda maior carga de HCV globalmente. Pela primeira vez no Paquistão, examinamos a correlação clínica de potenciais biomarcadores com HCV. Um estudo nacional foi realizado com 13.348 pacientes suspeitos de HCV de 2018 a 2022. Durante a era pré-COVID-19 de 2018 a 2019, a prevalência do HCV permaneceu em 30%. Durante 2018, entre pacientes positivos para HCV, 91% de ALT, 63% de AST, 67% de GGT, 28% de Bili T, 62% de HB, 15% de HBA1C, 25% de CREAT, 15% de PT, 15% de aPTT e 64% de AFP eram anormais. Durante 2019, entre os infectados pelo HCV, 74,47% de ALT, 63,54% de AST, 70,24% de GGT, 24,71% de Bili T, 8,77% de HB e 75% de AFP foram elevados. A TC/TAC revelou 4,65% de complicações hepáticas (leve 13,04%, moderada 30,43% e grave 56,52%). Durante 2020, a prevalência do HCV permaneceu em 25%. 65,17% de ALT, 64,20% de AST, 68,75% de GGT, 31,25% de Bili T, 20,97% de HB, 4,65% de CREAT e 73,68% de AFP estavam elevados. A análise de TAC revelou complicações hepáticas em 4,41% (14,81% leves, 40,74% moderadas e 44,44% graves). 85,71% dos participantes o diabetes estava fora de controle. Durante 2021, a prevalência de HCV permaneceu em 27,1%. Os níveis de ALT (73,86%), AST (50,6%), GGT (67,95%), Bili T (28,21%), HB (20%), CREAT (5,8%) e AFP (82,14%) estavam anormais. Durante 2022, os níveis de ALT (56,06%), AST (56,36%), GGT (56,6%), Bili T (19,23%), HB (43,48%), HBA1C (14,81), CREAT (18,92%), AFP (93,75%) eram anormais.

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A análise de TAC revelou 7,46% de complicações hepáticas (25% leves, 30,36% moderadas e 42,86% severas). Durante 2021 e 2022, 83,33% do diabetes do sujeito não foi controlado.

Palavras-chave: HCV, Paquistão, ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, marcadores tumorais, AFP, CEA, CA 125, CA 19-9, iPTH.

1. Introduction

Hepatitis C Virus infection is a major public health concern, worldwide. Over the period of last few decades, Pakistan has not seriously taken actions against HCV global challenge, causing its worst placement of second largest HCV burden, with 9.8 million people living with chronic HCV and millions of healthy people at risk of HCV infection through multiple risk factors prevailing in the community such as barbering, ear, nose piercing, blood transfusion, medical injections, or injecting drug use (WHO, 2022a, Waheed et al., 2010). To meet the sustainable development goals, by 2030, Pakistan need to treat at least 1.1 million HCV cases per year. However, the planning and development board of the Punjab government revealed massive challenges for management of national hepatitis elimination program and suggested that national or local authorities could not single handedly manage the proceedings, but requires further sincere assistance from international donors and supportive organizations to drive through the tough phase of HCV burden of disease in Pakistan (Chhatwal et al., 2019; WHO, 2022b).

In Pakistan, 12 million people were suffering from hepatitis and nearly 150,000 new cases were added each year (WHO, 2022a, Chhatwal et al., 2019). On average, half of all blood transfusions were not screened against infectious agents such as HCV, or HBV, or HIV (Chhatwal et al., 2019). The screening of general population has been challenging and scale-up of point-of-care testing is essentially required (WHO, 2022b). Improvements in HCV screening and treatment through advanced and early micro-elimination programs, community engagements, and decentralizing HCV treatment to multiple health sectors. Currently there is no vaccine available for HCV (Saeed et al., 2014). Since 2001 to 2011, ribavirin and interferon were the standard of care HCV infected patients (Saeed et al., 2015). However, recently several direct-acting antivirals were recommended by U.S. Food and Drug Administration (FDA) in combinations which showed significantly better response with minimal side reactions (Waheed et al., 2012).

HCV infections are augmenting gradually and there is dire need to carefully monitor the national HCV screening programs. Pakistan lacks the adequate HCV national surveillance program for continuous monitoring of daily HCV cases, successfully treated HCV patients, HCV related hepatocellular carcinomas and HCV related daily deaths (Khan et al., 2020; Saeed et al., 2017). Herein we first time correlated several important biochemical parameters among HCV infected individuals, enrolled at Islamabad Diagnostic Center with more than 100 branches in Pakistan during 2018 to 2022, and accurately determine the HCV prevalence *via* real-time PCR based advanced technologies. Furthermore we investigated the potential radiological findings through computed tomography in correlation with severe clinical manifestations of HCV infected patients.

2. Material and Methods

To investigate the clinical correlation of distinct biological markers in HCV infected patients, we conducted a cross-sectional study among 13,348 enrolled participants during the period of January 2018 to August 2022 at Islamabad Diagnostic Center having >100 branches in Pakistan. Pre-test counseling was performed by team of physicians, researchers and trained counselors and history and formal consent was obtained from each participant. The study was approved by the institutional review board committee and ethical review board. To estimate the choice of selection, participants voluntarily selected for HCV screening either *via* qualitative (Cobas Omni, 6800/8800 systems P/N: 06997546190 & 09051554190, ELISA based detection) or quantitative (Abbott antiHCV-08P06, real-time PCR based detection) methods. Discordant result samples were repeated. The ELISA based kits had no cross reactivity with other human viruses such as hepatitis B virus, Influenza viruses A/B, Coronavirus OC43, Cytomegalovirus, Respiratory Syncytial virus, Measels virus, Rotavirus, Norovirus, Mycoplasma pneumonia, Epstein-Barr virus, Adenovirus, Human metapneumovirus, Varicella Zosyer virus and Mumps virus. The standardized test kits were refrigerated and stored according to manufacturer's instructions (at 2-8 degree or -20 freezers as per standards, while extracted RNAs were stored at -70 deep freezer).

3. Results

13,348 suspected HCV infected patients were enrolled for the study. For HCV detection both quantitative (including real time PCR) and qualitative tests (including ELISA), were used according to kit manufacturers protocols. HCV genotype 3 remained predominant in Pakistan. During pre-COVID-19 era of 2018-2019, the prevalence of HCV remained 30%. However, during COVID-19 era of 2020 the prevalence of HCV dropped to 25%. During COVID-19 era of 2021, the HCV prevalence was determined 27.1%. While during COVID-19 era of 2022, the HCV prevalence was found 24.54%. To examine further, we retrospectively investigated the data during 2014-2018 and observed that HCV prevalence remained 39.9%. Compared to the HCV prevalence in 2014-2018, during the 2020 peak time of COVID-19 surge in Pakistan, the rate of prevalence decreased by approximately 1.6-fold. One of the possible explanations to the rapid decrease in HCV prevalence rate during COVID-19 era might be due to strict lock-down policies and lack of out-patient department in hospitals, the attention of physicians was more inclined towards attending SARS-CoV-2 patients, which caused nation-wide negligence in attending patients infected with HCV and other life-threatening pathogens.

To examine the clinical correlation of HCV with biomarkers, we evaluated alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), Total Bilirubin (Bili T), hemoglobin (HB), hemoglobin A1C (HBA1C), Creatinine (CREAT), prothrombin time (PT), activated partial thromboplastin clotting time (aPTT) and Tumor Markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), and intact parathyroid hormone (iPTH). The severity of disease was also examined through distinct radiological findings examined *via* computed tomography (CT or CAT) scan of liver, among patients with severe abnormalities in ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, and tumor markers AFP, CEA, CA 125, CA 19-9, and iPTH.

During the pre-COVID-19 era in 2018, among 3389 enrolled participants, 43.65% were males and 56.35% were females. 42.85% of the enrolled participants screened for HCV *via* real-time PCR based quantitative detection method while 57.15% relied on initial screening through ELISA based qualitative detection method. The real-time PCR based confirmed HCV positive patients were included for clinical correlation of potential ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT biomarkers and AFP tumor-marker. Among enrolled participants significant abnormalities were determined. Among real-time HCV positive patients, 91% of ALT, 63% of AST, 67% of GGT, 28% of Bili T, 62% of HB, 15% of HBA1C, 25% of CREAT, 15% of PT and 15% of aPTT remained abnormally raised. The computed tomography analysis revealed liver complications among 4.55% participants. Among patients with liver complications, 16% show mild liver complications, 35% moderate and 49% showed sever liver complications. 64% of tumor marker AFP levels showed abnormally raised levels. Among patients with raised AFP levels, other tumor biomarkers including CEA, CA 125, CA 19-9, and iPTH were also raised. Among most of the patients undergoing anti-viral treatment option Sofosbuvir, Valpatasvir, and Siliver were recommended by majority of physicians.

Similarly, during 2019 pre-COVID-19 phase, among 3302 enrolled participants, 44.3% were males and 55.7% were females. 42.03% of the enrolled participants screened for HCV *via* real-time PCR based quantitative detection, however 57.97% preferred ELISA based qualitative detection. The real-time PCR based confirmed HCV patients were investigated for clinical correlation of potential biomarkers. The analysis revealed that among real-time HCV positive patients, 74.47% of ALT, 63.54% of AST, 70.24% of GGT, 24.71% of Bili T and 8.77% of HB were abnormally higher. The CT/CAT scan revealed liver complications among 4.65% individuals (including mild 13.04%, moderate 30.43% and severe 56.52% complications). 75% of tumor marker AFP remained abnormally raised. Among patients with raised AFP levels, other tumor biomarkers including CEA, CA 125, CA 19-9, and iPTH were also significantly raised. Among most of the patients undergoing anti-viral treatment option Siliver, Sofosbuvir & Valpatasvir, Ribavirin, Valpatasvir & Sofosbuvir were recommended by majority of physicians depending upon patient's conditions.

The COVID-19 surge took occurred in 2020 in Pakistan. In 2020, due to sudden rise in SARS-CoV-2 cases most of the physicians shifted their preference towards treatment of SARS-CoV-2 and outpatient departments remained closed for several months causing limited diagnosis of other viral infections. Compared to the average flow rate of HCV suspected patients during pre-COVID-19 phase, during 2020 the patient flow decreased by 0.8%. Among 2703 enrolled participants, 43.99% were male and 56.01% were female. 34.78% participants preferred real-time PCR based detection for HCV, while 65.22% preferred ELISA based qualitative tests for detection. The real-time PCR based confirmed HCV positive patients were investigated for clinical correlation of potential biomarkers. The analysis revealed that among real-time HCV positive patients, 65.17% of ALT, 64.20% of AST, 68.75% of GGT, 31.25% of Bili T, 20.97% of HB and 4.65% of CREAT were abnormal. The CT/CAT scan revealed liver complications among 4.41% individuals (including 14.81% mild, 40.74% moderate, and 44.44% sever complications). 73.68% of tumor marker AFP remained abnormally raised. Among patients with raised AFP levels, other tumor biomarkers including CEA, CA 125, CA 19-9, and iPTH were also found raised. Uncontrolled diabetes was reported among 85.71% subjects while controlled diabetes was reported among 14.29% patients. Among most of the patients undergoing anti-viral treatment option Covmed, Siliver, Sofosbuvir & Valpatasvir, Hepamerz, Siliver & Hepamerz were recommended by by majority of physicians depending upon patient's conditions.

During 2021, among 3954 enrolled participants, 43.2% were male and 56.8% were females. 56.75% participants preferred real-time based detection for HCV, while 43.24% preferred ELISA based detection. The real-time PCR based confirmed HCV positive patients were investigated for the clinical significance of aforementioned biomarkers. Among HCV positive patients, the levels of ALT (73.86%), AST (50.6%), GGT (67.95%), Bili T (28.21%), HB (20%) and CREAT (5.8%) remained abnormally raised. The CAT scan revealed liver complications among 2.89% individuals (including mild 7.14%, moderate 28.57% and severe 64.29% complications). 82.14% of AFP were abnormally higher. However, during 2022 (till 30th August), the levels of ALT (56.06%), AST (56.36%), GGT (56.6%), Bili T (19.23%), HB (43.48%), HBA1C (14.81) and CREAT (18.92%) remained abnormally raised, as shown in Figure 1. The CT/CAT scan revealed liver complications among 7.46% individuals (including 25% mild, 30.36% moderate, and 42.86% sever complications). 93.75% of tumor marker AFP levels were abnormally raised. Among patients with raised tumor marker AFP levels, other biomarkers including CEA, CA 125, CA 19-9, and iPTH were also elevated. Uncontrolled diabetes was reported (during 2021-2022) among 83.33% subjects while controlled diabetes was reported among 16.67% patients. Among most of the patients undergoing anti-viral treatment option Covmed, Sofosbuvir & Valpatasvir, Hepamerz & Siliver, Daclatasvir & Sofosbuvir &Ribazole, Sofosbuvir & Ribavirin, Engerix & Rebecid, Engerix & Amovax, were recommended by majority of physicians depending upon patient's conditions.

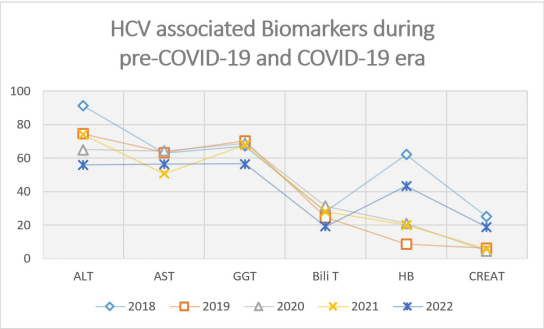

Figure 1. Clinical association of biological markers in HCV infected patients.

4. Discussion

Viral infections are increasing day by day. To cope up the targets of sustainable development goals of hepatitis elimination by 2030, accurate HCV diagnosis among general population and scale-up of point-of-care testing are essentially required. Identification of potential biomarkers and associated molecular pathways, can be critical for management of viral infections in time and might prevent viral spread (GBD 2019 Hepatitis B Collaborators, 2022; Polaris Observatory HCV Collaborators, 2022; Safi et al., 2012; Piracha et al., 2018, 2020; GBD 2019 Adolescent Young Adult Cancer Collaborators, 2022; Global Burden of Disease 2019 Cancer Collaboration, 2022; Saeed et al., 2022a, b, c, 2023). In Pakistan, the prevalence of HCV varies with respect to risk factors and type of population. Here in, we enrolled general population for the clinical evaluation of potential biomarkers among HCV infected individuals. The national prevalence of HBV in Pakistan was 2.5% in 2008 (Saeed et al., 2015).

Recently, there have been great advancements in the treatment of HCV and almost each year a new drug was approved which was more effective than the previous ones. After the classical treatment with Interferon and later Pegylated Interferon, a new very effective drug came named Sovaldi which proved to be very effective and is also in use in Pakistan. Few other drugs also approved later like Harvoni and Epclusa and their treatment efficiency is more than 90%. The patients have to take these drugs from 2-6 months for cure. Mavyret drug can treat all the genotypes of Hepatitis C in only 2 months. The aforementioned drug have NS3/4A protease inhibitor and NS5A inhibitor hence it is effective for all major genotypes of HCV. The recommended treatment length depends on viral genotype, cirrhosis status, previous HCV treatment, general health status of the patient as sometime the patient has to take this drug for longer duration. The drug also proved to be effective for those who were previously treated but without cure. For the approval of Mavyret, clinical trials were done with treatment duration of 2, 3 and 4 months on 2300 patients (suffering from different HCV genotypes) in 27 countries. The studies include those without cirrhosis, with compensated cirrhosis, with severe chronic kidney disease and those who were not previously treated with direct-acting antivirals (DAA) treatment. The results were surprising as a cure rate of 92 to 100% was achieved (Livertox: Clinical and Research Information on Drug-induced Liver Injury, 2012).

Our study revealed that during 2014 to 2018, the prevalence rate of HCV in general population was 39.9%, indicating alarmingly huge rise in number of HCV positive cases over the passage of one decade. During the 2020, the HCV prevalence apparently dropped to 24.54% by 1.6-folds, possibly due to overall reduction in flow of out-patient department. Interestingly, during the course of multiple waves of SARS-CoV-2 epidemics in Pakistan (during 2020 to 2022), among confirmed HCV positive patients on antiviral medications, the SARS-CoV-2 infection was not reported, one of the possible explanation could be that the HCV patients were already on antiviral treatment. However among the enrolled participants, upon the HCV course of infection, uncontrolled diabetes was reported in majority. Previously, we evaluated the clinical association of SARS-CoV-2-positive patients with several important biochemical parameters including C-reactive protein, D-dimer, ferritin, hemoglobin A1c, interleukin 6, lactate dehydrogenase, NT-pro-B-type natriuretic peptide, and procalcitonin and further analyzed associated radiological findings through high-resolution computed tomography during the COVID-19 epidemics in Pakistan (Saeed et al., 2022a, b). However, herein for the first time from Pakistan, we demonstrated national data during 2018 to 2022, on the clinical significance of various important biochemical parameter abnormalities, including alanine transaminase, aspartate aminotransferase, gamma-glutamyl transferase, total Bilirubin, hemoglobin, hemoglobin A1C, Creatinine, prothrombin time, activated partial thromboplastin clotting time and tumor Markers including alpha-fetoprotein, carcinoembryonic antigen, cancer antigen 125, cancer antigen 19-9, and intact parathyroid hormone among HCV infected individuals. Due to limitations of our study, we could only examine HBA1C to determine diabetes related comorbidities among HCV infected individuals. However in future studies, it would be more interesting to further investigate comorbidities in HCV infecting individuals by examining patient's lipid profile tests including level of triglycerides, HDL cholesterol and LDL cholesterol in correlation to AFP, GGT; investigating ultrasound signs of portal hypertension, ascites related comorbidities, and high resolution computed tomography mediated analysis of disease progression.

5. Conclusion

Current study revealed that during HCV course of infection, ALT, AST, GGT, Bili T, HB, HBA1C, CREAT, PT, aPPT, and tumor markers AFP, CEA, CA 125, CA 19-9, and iPTH biomarkers showed positive correlation with mild-moderate and severe liver conditions irrespective of SARS-CoV-2 waves during 2020-2022. Current study is important for physicians and world health strategic organizations. Furthermore, it would be critical to determine the impact of multiple antiviral HCV drugs on these biomarkers in future. Also, this study would further open doors of clinical investigations among HCV patients with repeated histories of infections.

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