COLORECTAL CANCER SCREENING TO IDENTIFY UNDIAGNOSED HEPATITIS C IN AN AUSTRIAN COHORT

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SUMMARY

Objectives: Hepatitis C virus (HCV) infection remains a significant public health concern despite the introduction of direct acting antiviral agents. To reach the World Health Organization (WHO) goal of eliminating viral hepatitis as a public health threat by 2030, adequate screening strategies and early diagnosis are crucial. This study aimed to determine the prevalence of HCV infection in an Austrian cohort and assess the feasibility of incorporating HCV screening into colorectal screening programmes.

Methods: The study enrolled 1,894 asymptomatic individuals during a colorectal screening programme with a mean age of 57 (± 7 years) years. Sera of the participants were screened for HCV-specific antibodies, and blood samples of individuals with detectable HCV-specific antibodies were tested by the polymerase chain reaction (PCR) to confirm a chronic HCV infection. Furthermore, we evaluated the characteristics of these individuals including their anthropometrics, biomarkers, and liver-specific information such as those obtained with a fibroscan.

Results: We found that 14 (0.74%) of the participants had detectable levels of HCV-specific antibodies, with 6 (0.32%) individuals being newly diagnosed with a chronic HCV infection. One of the 6 patients showed signs of liver cirrhosis. The newly diagnosed individuals included 4 cases of HCV genotype 1a and 2 cases of 1b.

Conclusion: Our study highlights the importance of screening for HCV infection in asymptomatic individuals, not only for those at risk of HCV exposure or with elevated liver enzymes. Incorporating HCV screening into colorectal screening programmes could be an effective strategy for increasing the rate of HCV diagnosis, thereby improving public health outcomes. Further investigation is needed regarding cost-effectiveness and strategies to reach individuals who have no access to screening programmes or do not adhere to regular preventive screenings.

Key words: chronic HCV infection, HCV screening, population-based screening, HCV, HCV genotype

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INTRODUCTION

Hepatitis C virus (HCV) infection remains a major public health concern with approximately 72 million affected globally (1). Since the discovery of HCV in 1989, the virus continues to pose a significant challenge for public health, particularly in terms of its ability to cause chronic liver disease, increase the risk of liver cirrhosis, hepatocellular carcinoma and liver disease-related death. Individuals at increased risk for chronic HCV infection include those with a history of intravenous drug abuse, blood transfusions before 1992, prisoners, nosocomial infections, and men who have sex with men (2–5).

The World Health Organization (WHO) has set the ambitious goal to eliminate HCV infection by 2030, which includes reducing the incidence of HCV infections by 90%, reducing HCV-associated mortality by 60% and treating 80% of people with chronic HCV-infections (6). The prevalence of HCV infection has declined in recent years with the introduction of direct-acting antiviral agents, although a vaccine for HCV remains elusive (7). However, current trends suggest we are unlikely to meet the WHO's elimination goals. This is supported by a modelling study analysing global changes in HCV prevalence between 2015 and 2020 (8).

The current global HCV diagnosis rate remains low, with an estimated 20% of all cases being detected (9). In the European Union (EU) and the United States (US), the diagnosis rate is slightly higher, at 36% and 50%, respectively (10). The US Preventive Services Task Force (USPTF) guidelines recommended screening for HCV infections in all adults (11). However, reaching all

adults remains difficult, and therefore incorporating HCV analysis into other screening programmes may be a pragmatic solution.

One potential strategy is to determine HCV infection during a colorectal screening programme (12). Colorectal cancer is a common and potentially preventable disease, with screening programmes available in many developed countries (13), although their systematic implementation varies even across Europe. In Austria, only a few federal states currently offer organized colorectal screening programmes, and there is a lack of comprehensive data on the utilization rates in the general population (14). Efforts should be made to expand these programmes nationwide in the future. By incorporating HCV screening into these programmes, it may be possible to increase the rate of HCV diagnosis and ultimately improve public health outcomes.

The aim of this study was to gather data on the overall prevalence of HCV infection in two Austrian cohorts of asymptomatic individuals and to assess the feasibility of incorporating HCV screening into a colorectal screening programme. Furthermore, it was determined how many patients newly diagnosed with HCV would have been further assessed after common liver screening using a fibrosis index based on four factors (Fib-4) and an aspartate aminotransferase-to-platelet ratio index (APRI).

MATERIALS AND METHODS

As part of the colorectal carcinoma (CRC) screening programme (SAKKOPI) and the health screening programme (SAPHIR) in the cities of Oberndorf and Salzburg, Austria, 1,894 asymptomatic individuals were examined for hepatitis C virus infection (SAKKOPI n = 906 and SAPHIR n = 988) between January 2007 and March 2020. Patients were selected for screening through colonoscopy according to their age. The study and all procedures were performed according to the principles of the Declaration of Helsinki. The local Ethics Committee for the Province of Salzburg approved the study protocol (approval no. 415-E/1262). Written informed consent was obtained from every participant.

To screen for liver disease, the individuals underwent medical history evaluations, liver enzyme tests were performed, and a subset of the participants (n = 1,179) also underwent transient elastography evaluating liver stiffness analysed in kPa performed by specialists in internal medicine. Blood was collected at the participating hospitals, including the General Hospital in Oberndorf and the University Hospital Salzburg. Liver enzymes including bilirubin, gamma-glutamyl transferase (gGT), aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (AP) were analysed.

Fib-4 and APRI scores were calculated. Fib-4 is a non-invasive score to estimate liver scarring in HCV and HBV patients to assess need for biopsy (15). APRI represents the AST to platelet ratio index determining the likelihood of hepatic fibrosis in patients with a chronic HCV-infection (16).

Serum samples were collected using a standard blood drawing system, centrifuged after a coagulation time of 30 minutes and stored at −80 °C. The presence of HCV-specific IgG antibodies was determined using enhanced chemiluminescence-immunoassay technology (CLIA) with the Vitros Anti-HCV MicroWell test (Ortho Clinical Diagnostics/Grifols, Bridgend, UK) on the VITROS™ ECiQ Immunodiagnostic System (Ortho Clinical Diagnostics, Bridgend, UK). Patients who tested positive for HCV-specific IgG were further evaluated for HCV RNA and genotype. The amplified PCR products were subjected to real-time PCR using HCV genotype-specific probes and analysed using a real-time PCR instrument. The genotyping results were analysed and compared with the HCV genotyping database to determine the HCV genotype(s) present in the patient samples.

Stata 18 was employed for the entirety of our statistical analyses. For continuous variables, we presented the data as either mean and standard deviation (SD) for those following a normal distribution, or as mean and interquartile range (IQR) for those not normally distributed. The normality of distribution for these variables was rigorously assessed using the Kolmogorov-Smirnov test. We also analysed categorical data. For this purpose, the chi-square test was utilized to compare frequencies and assess associations between different categorical variables.

All other data, including anthropometrics, biomarkers, and liver-specific information, were acquired as described previously (17, 18).

RESULTS

Total Cohort

The study included 1,894 participants with a mean age of 57 years (± 7 years). A total of 935 (49%) of subjects were males and 955 (51%) were females; 598 (31%) of the patients showed signs of a metabolic syndrome according to current diagnostic criteria (19). The mean Fib-4 score was 1.07 (± 0.58), mean platelet count was 247 (G/L) (± 56), and mean liver stiffness measured by transient elastography was 5 kPa (± 3) (Table 1).

Patients with Positive HCV Antibodies

Out of the above-described participants, 14 (0.74%) individuals had detectable levels of HCV-specific antibodies. Five had

Table 1. *Characteristics of the total cohort (N = 1,894)*

Sex, n (%)	
Male	935 (49)
Female	955 (51)
Age (years), mean (SD)	57 (7)
BMI, mean (SD)	27 (5)
Metabolic syndrome, n (%)	598 (31)
Bilirubine (mg/dL), mean (SD)	0.9 (0.6)
gGT (U/L), mean (SD)	34 (40)
AP (U/L), mean (SD)	65 (19)
AST (U/L), mean (SD)	23 (10)
ALT (U/L), mean (SD)	25 (16)
Platelets (G/L), mean (SD)	247 (56)
Fib-4, mean (SD)	1.07 (0.58)
LSM (kPa), mean (SD)	5 (3)

SD – standard deviation; gGT – gamma-glutamyl transferase; AP – alkaline phosphatase; AST – aspartate transaminase; ALT – alanine transaminase; LSM – liver stiffness measurement

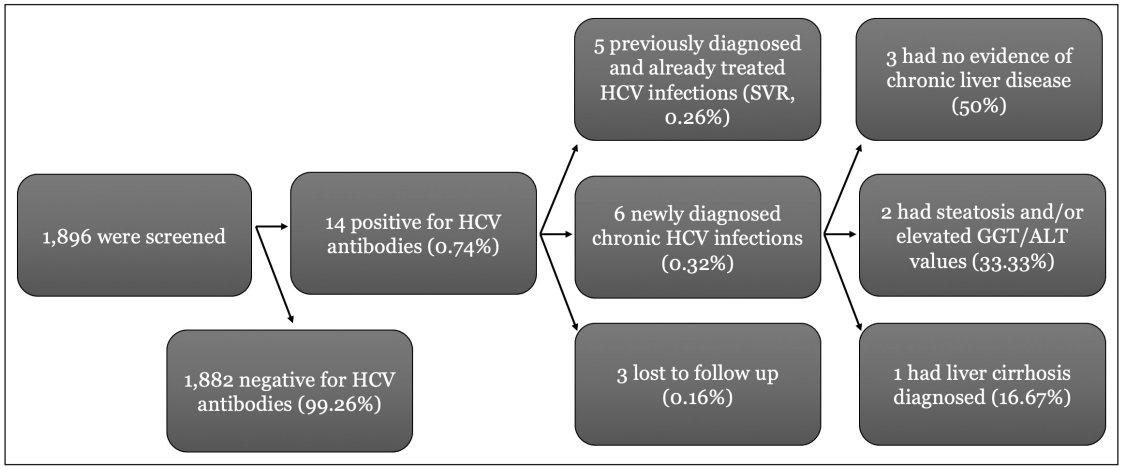

Fig. 1. *Flowchart.*

Source: own presentation

previously been diagnosed and successfully treated, while three were lost to follow-up (Fig. 1). Reflex testing of HCV RNA in anti-HCV positive individuals would have prevented the loss to follow-up of three patients.

The remaining 6 (0.32%) individuals were newly diagnosed with chronic HCV infection. Out of these 14 individuals, six patients had a Fib-4 below 1.3, seven patients had a Fib-4 ≥ 1.3 and < 2.67, and one patient displayed a Fib-4 ≥ 2.67, indicating advanced liver fibrosis/cirrhosis (Fig. 2). One individual (7.1%) was infected after blood plasma donation. The suspected route of transmission for three patients (17.6%) were red blood cell transfusions, and for ten individuals (71.4%) it is unknown.

Newly Diagnosed Viraemic HCV Patients

Of note, of the six newly diagnosed HCV-positive patients with a mean age of 60 (± 4.75), one had liver cirrhosis (Fib-4 > 2.67, APRI > 1.5), one had a Fib-4 between 1.3 and 2.67, and an APRI between 0.5 and 1.5, and three had both an APRI < 0.5 as well as Fib-4 < 1.3. The mean Fib-4 score was 1.2 (± 0.64), we observed no statistically significant difference in Fib-4 between HCV-positive patients and the total cohort (p = 0.17). Two individuals were infected after RBC transfusions, one patient became infected after blood plasma donation and for the remaining three individuals the route of transmission remains unknown.

Transient elastography was performed for all newly diagnosed viraemic HCV patients: the mean liver stiffness measured was 4.7 kPa (± 1.62) and mean CAP score in dB/m was 270.5 (± 47.25). Only the patient with liver cirrhosis (28 kPa) showed a liver stiffness measurement above 8 kPa. The genotype distribution among these newly diagnosed individuals showed four cases of HCV-genotype 1a and two cases of 1b. Further characteristics of the newly diagnosed viraemic patients are shown in Table 2.

DISCUSSION

We found that fourteen of the participants had detectable levels of HCV-specific antibodies, with six individuals being newly diagnosed with a chronic HCV infection. The mean age and gender distribution of the newly diagnosed individuals suggests that HCV infection is affecting a wide range of the population,

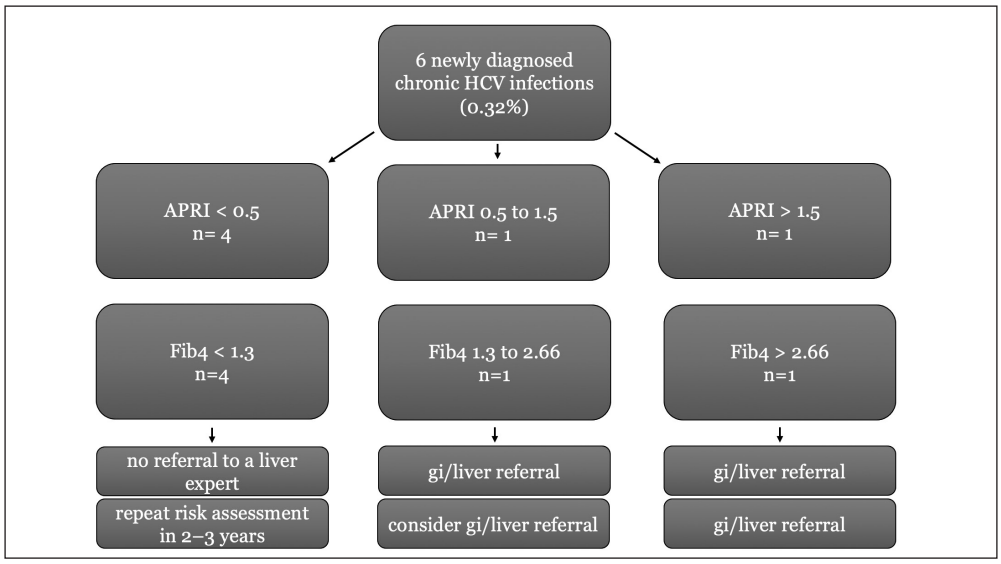

Fig. 2. *Further testing according to Fib-4 and APRI (16).*

Source: own presentation

Table 2. *Characteristics of the newly diagnosed viraemic patients*

Suspected route of transmission	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
	RBC transfusion	Blood plasma donation	RBC transfusion	Unclear	Unclear	Unclear
Genotype	1b	1a	1a	1a	1b	1a
Age (years)	58	64	58	62	63	49
Sex	Female	Male	Female	Male	Female	Female
BMI	27	23	21	28	NA	23
Fib-4	0.83	7.8	1.66	1.26	1.2	0.61
Bilirubin (mg/dL)	1.3	1.8	0.9	0.9	0.6	0.6
gGT (U/L)	23	356	25	23	17	14
AST (U/L)	45	89	30	24	24	14
ALT (U/L)	73	58	27	20	24	18
AP (U/L)	65	295	59	45	94	65
LSM (kPa)	4.8	27.7	3.7	4.6	3.7	5.8
Platelets (G/L)	367	96	200	264	256	267
CAP (dB/m)	306	217	254	287	351	220
Fib-4	0.83	7.79	1.67	1.26	1.21	0.61

BMI – body mass index; gGT – gamma-glutamyl transferase; AST – aspartate transaminase; ALT – alanine transaminase; AP – alkaline phosphatase; LSM – liver stiffness measurement; CAP – controlled attenuation parameter; Fib-4 – fibrosis index based on four factors

and some individuals may still go undiagnosed. Direct-acting antiviral agents' treatment is effective and associated with the minimization of de novo HCV-related hepatocellular carcinoma and liver related mortality (20).

The high prevalence of steatosis among these individuals and the fact that one asymptomatic patient was diagnosed with liver cirrhosis highlights the importance of screening for liver disease in HCV-infected individuals. Four of the six newly diagnosed patients had an APRI < 0.5, and they would not undergo screening for liver disease based on the recently proposed Structured Early detection of Asymptomatic Liver Cirrhosis (SEAL) algorithm (21). This emphasizes the need for further examination of screening approaches in asymptomatic individuals, as certain chronic HCV-infections could evade diagnosis by non-invasive diagnosis scores. We observed no statistically significant difference in Fib-4 between HCV-positive patients and the total cohort. This lack of statistical significance is likely attributable to the limited sample size inherent to our real-life clinical data.

The distribution of HCV-genotypes in this study was slightly different from previous reports. In previous Austrian population studies, genotype 1b was more common than genotype 1a. In contrast, in this study among newly diagnosed individuals, HCV genotype 1a was found in four out of six individuals (66.7%) and 1b was found in two out of six individuals (33.3%). This might be due to social changes including intense touristic activities, war and immigration (22, 23). One newly diagnosed patient, now 66 years old, likely acquired the virus through plasma cell donation in Salzburg, where infections occurred due to poor hygiene and safety measures during the 1970s and 1980s (24–26).

In the United States a systematic screening for all individuals aged 18–79 years at least once in a lifetime is recommended (11). In Germany, the opportunity for a one-time screening for hepatitis B and C is established for all individuals above the age of 35, and pregnant women are also screened at the beginning of prenatal care (primarily as a surrogate group for population screening) (27). To achieve the WHO goal of 90% diagnosed individuals by 2030, a population-based screening was found to be cost-effective in France (28). Austria, as a central European country, is likely to be comparable to France in this regard. However, there is currently a lack of public screening strategies for chronic HCV infection in Austria. Recommended screening strategies for colorectal carcinoma in Austria are already established: individuals aged 45–75 should have the opportunity to undergo colorectal cancer screening every ten years through colonoscopy or every two years through a faecal occult blood test (29). Unfortunately, the participation rates in CRC screening are not comprehensively documented in Austria. The general screening utilization varies widely across Europe, ranging from 6.3% to 75.4% depending on the type of screening programme offered (30).

The strength of our study includes the detailed characterization of the cohort, as there is no comparable population-based data set available for Austria.

CONCLUSION

Incorporating a one-time screening for HCV into pre-existing colorectal cancer screening programmes could be beneficial. However, the effectiveness of such integration may be limited by low participation rates and the fact that healthier individuals, who are more likely to participate in screenings, may not represent the highest risk groups for HCV. Further studies are necessary to assess the practicality and cost-effectiveness of integrating HCV screening into CRC screening programmes and to develop strategies that reach underserved populations. By analysing these factors in a broader context, we can better understand the potential impact of such integrated programmes and work towards improving HCV diagnosis and treatment outcomes.

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Conflicts of Interest

None declared

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Authors' Contributions

All authors contributed substantially to this manuscript. HH and SB contributed equally to this work.

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