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Clinical features and comorbidity pattern of HCV infected migrants compared to native patients in care in Italy: A real-life evaluation of the PITER cohort

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ABSTRACT

Background: Direct-acting antivirals are highly effective for the treatment of hepatitis C virus (HCV) infection, regardless race/ethnicity. We aimed to evaluate demographic, virological and clinical data of HCV-infected migrants vs. natives consecutively enrolled in the PITER cohort.
Methods: Migrants were defined by country of birth and nationality that was different from Italy. Mann-Whitney U test, Chi-squared test and multiple logistic regression were used.
Results: Of 10,669 enrolled patients, 301 (2.8%) were migrants: median age 47 vs. 62 years, ($p < 0.001$), females 56.5% vs. 45.3%, ($p < 0.001$), HBsAg positivity 3.8% vs. 1.4%, ($p < 0.05$). Genotype 1b was prevalent in both groups, whereas genotype 4 was more prevalent in migrants ($p < 0.05$). Liver disease severity and sustained virologic response (SVR) were similar. A higher prevalence of comorbidities was reported for natives compared to migrants ($p < 0.05$). Liver disease progression cofactors (HBsAg, HIV coinfection, alcohol abuse, potential metabolic syndrome) were present in 39.1% and 47.1% ($p > 0.05$) of migrants and natives who eradicated HCV, respectively.

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Conclusion: Compared to natives, HCV-infected migrants in care have different demographics, HCV genotypes, viral coinfections and comorbidities and similar disease severity, SVR and cofactors for disease progression after HCV eradication. A periodic clinical assessment after HCV eradication in Italians and migrants with cofactors for disease progression is warranted.

Introduction

Chronic infection with hepatitis C virus (HCV) is a global public health challenge and a leading cause of liver disease-related morbidity and mortality. It has been estimated that over 71 million people have chronic hepatitis C infection, mainly among populations of Eastern Mediterranean and European Regions [1–4]. Persistent HCV infection is associated with the development of hepatic cirrhosis, hepatocellular carcinoma, liver failure and death [5,6].

Based on European Center for Disease Prevention and Control (ECDC) data [7], 14% of all chronic HCV hepatitis in Europe, and about 5% in Italy, affect migrants. It has been reported that Italy is the country with the highest prevalence rate of HCV in general population in Europe [8], whereas representative data on HCV prevalence rate in migrants are not available.

The availability of the second-generation direct acting antivirals (DAAs) has led to a high rate of HCV eradication. DAAs achieve cure rates over 98% in both clinical trials and real-world practice [9–11] regardless of race/ethnicity and HCV genotypes [12,13]. In patients without cirrhosis who achieve an SVR, the HCV infection can be considered as definitively cured. However, EASL Clinical Practice Guidelines suggest that patients with pre-existing cofactors for liver disease (notably, history of excessive alcohol drinking, obesity and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment, as needed [12]. The presence of cofactors for liver disease progression is common in patients with HCV who receive antiviral therapy in Italy, and might be different in the migrant population in care. Only few studies have examined the clinical profile of the linked to care foreign-born HCV infected patients. Thus, the aim of this study was to evaluate demographic, virological and clinical data of HCV-infected migrants in care in Italy as compared to native Italians. In particular, we aimed to underline the pattern of comorbidities and other factors for liver disease progression that should be focused in the clinical practice after HCV eradication.

Methods

Patients

Patients' data from the Italian Platform for the study of viral hepatitis therapy (PITER) cohort [14] between April 2014 and June 2019 were evaluated.

For each consecutively enrolled patient, baseline demographic, clinical and laboratory characteristics were recorded prior to the start of treatment. Migrants were defined as persons with country of birth and nationality different from Italy, whereas natives include persons born in Italy and with Italian nationality.

Fibrosis stage was defined based on liver transient elastography data, which were considered as validated if each patient had at least 10 available stiffness measurements, with a success rate of at least 80%, an interquartile range of less than 30% of the median stiffness score, and a body mass index (BMI) of $<30\,kg/m^2$ [15]. Liver cirrhosis was defined when the stiffness score was equal to or higher than 14 kPa or according to biochemical and instrumental data of portal hypertension [15]. Decompensated cirrhosis was diagnosed according to the presence or appearance of ascites and/or gastrointestinal bleeding due to portal hypertension and/or hepatic encephalopathy and/or icterus and/or and spontaneous bacterial peritonitis.

Regarding the presence of cofactors for liver disease progression, the available data collected in the electronic case report form during the enrollment and following HCV eradication were evaluated Specifically: potential metabolic syndrome (i.e. the presence of ultrasound fat and hypertension/cardiovascular disease or type 2 diabetes or BMI$>25\,kg/m^2$ in patients who did not report), HBsAg positivity, HIV coinfection or current alcohol abuse (defined as 63 drinking more than 3 alcohol units/day [16]) were considered as cofactors for liver disease progression after HCV eradication.

Statistical analysis

Age at baseline was reported as median and ranges and all other categorical variables as proportions (N and %). The Mann-Whitney U test was used to assess differences between age distribution and the Chi-squared test was used for comparison among proportions. A p-value <0.05 was considered statistically significant.

Adjusted Odds Ratios for potential confounding variables (i.e. age, sex, BMI, HCV genotype, HBsAg positivity, HIV coinfection, alcohol use, previous interferon-based treatment, liver stiffness value) were calculated by multiple logistic regression using migrant status as the dependent variable.

All analyses were performed using the STATA/SE 16.1 statistical package (StataCorp LP, College Station, TX, USA).

Ethics

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved by the Ethics Committee of the Istituto Superiore di Sanità (Italian National Institute of Public Health) and by the local Ethics committees of each clinical center. Patients' data were evaluated through an anonymous analysis, adopting codes generated by the electronic case report forms. All patients gave their written informed consent to participate in the study.

Results

Baseline characteristics of the study population

Among the 10,669 subjects included in PITER cohort, 301 (2.8%) were migrants: 76 (25.2%) from Africa; 33 (11%) from Asia; 5 (1.7%) from America; 187 (62%) from Europe, 96.8% of whom ($n=181$) from East Europe. Romania ($n=79$, 26.2%), Egypt ($n=57$, 18.9%), Moldova ($n=49$, 16,3%) and Ukraine ($n=33$, 11%) were the main country of origin.

Demographic, virological and clinical characteristics of migrants compared to the native patients are shown in Table 1.

Table 1
Migrant and native patients baseline characteristics.

Characteristics		Migrants ($N = 301$*)		Natives ($N = 10,368$*)		p**	Adjusted*** O.R. (95% C.I.)
		Median	Range	Median	Range		
Age (years)		47	18–78	62	18–95	< 0.001	0.92 (0.91–0.93)
		N.	%	N.	%	p****	
Sex	Male (Ref.)	131	43.5	5670	54.7	< 0.001	
	Female	170	56.5	4698	45.3		2.49 (1.73–3.56)
BMI	Normal (Ref.)	125	41.5	5078	49.0	< 0.05	
	Underweight	8	2.7	188	1.8		1.03 (0.40–2.66)
	Overweight-Obese	168	55.8	5101	49.2		2.26 (1.58–3.24)
Genotype	≠ 4 (Ref.)	229	79.5	9081	94.0	< 0.001	
	4	59	20.5	578	6.0		2.51 (1.60–3.93)
HBsAg+	No (Ref.)	229	96.2	7967	98.6	< 0.05	
	Yes	9	3.8	113	1.4		2.67 (1.22–7.24)
HIV+	No (Ref.)	183	94.8	5110	90.8	> 0.05	
	Yes	10	5.2	517	9.2		0.29 (0.11–0.71)
Alcohol use	Never (Ref.)	203	68.4	6562	64.4	> 0.05	
	Current	48	16.2	1661	16.3		0.84 (0.53–1.33)
	Past	46	15.5	1969	19.3		0.70 (0.43–1.15)
Previous	No (Ref.)	242	80.4	7593	73.2	< 0.05	
Interferon	Yes	59	19.6	2775	26.8		0.82 (0.55–1.24)
Liver Stiffness	≤ 14 KPa (Ref.)	220	73.1	6344	61.2	< 0.001	
value	> 14 KPa§	81	26.9	4024	38.8		1.14 (0.77–1.71)

* For some variables inconsistencies are due to missing values.
** p value Mann–Whitney rank-sum test.
*** Adjusted for all variable listed in table.
**** p value Chi-square test.
§ Patients with liver cirrhosis diagnosed by clinical and/or instrumental findings for whom liver stiffness measurement was not available were included in the group >14 KPa.

Migrants were significantly younger (median age of 47 vs. 62, $p < 0.001$) and more frequently females (56.5% vs. 45.3%, $p < 0.001$) compared to Italians. Of 301 migrants, 168 (55.8%) were overweight or obese (defined as having a BMI of ≥ 25 Kg/m^2) while natives were equally distributed between the normal (49%) and the overweight/obese group (49.2%).

No significant differences among migrants and native patients were observed for baseline alanine transaminase (ALT), aspartate transaminase (AST), platelet count, serum albumin, bilirubin, creatinine and international normalized ratio (INR) value (data not shown).

Genotype 1b was prevalent in both groups (53.5% and 48.9%, in migrants and natives respectively, $p > 0.05$). Genotype 1a and 2 were more frequently observed in native compared to migrant patients (12.1% vs. 6.6% and 19.1% vs. 5.2%, respectively) whereas genotype 4 was more frequent in migrants compared to natives (20.5%, vs. 6.0%, respectively) ($p < 0.001$).

No difference was found in the prevalence of anti-HBc positivity (anti-HBc$^+$/HBsAg$^-$) between migrants and natives (35.7% vs. 31.7%, respectively). A significantly higher HBsAg prevalence was detected in migrants (3.8%) compared to natives (1.4%) ($p < 0.05$).

After adjusting for potential confounding variables, HIV coinfection was significantly higher in native compared to migrant patients (OR: 0.29, 95% CI:0.11–0.71).

A higher prevalence of previous interferon-based treatment was reported for native compared to migrant patients (26.8% vs 19.6%, respectively; $p < 0.05$), nevertheless no difference was observed after adjusting for potential confounding variables.

Overall, 81 (26.9%) migrants and 4024 (38.8%) natives had liver cirrhosis diagnosis (liver stiffness value >14 KPa) ($p < 0.001$). However, this difference was not observed after adjusting for all variables considered by logistic regression analysis.

A similar C-P class distribution (C-P class A: 87% vs 82.2%; C-P class B/C: 13% vs. 17.8% in migrants and natives, respectively, $p > 0.05$) and a similar prevalence of decompensated cirrhosis (9.9% in migrants and 17.4% in natives, $p > 0.05$) were observed in both groups.

Similar rates of SVR12 were observed in migrants (98%) and natives (96%) patients ($p > 0.05$).

A comparison between migrants from East Europe vs others is shown in Supplementary Material. Migrant from East Europe were more frequently females and have different genotype pattern versus migrants from other geographical area, 50.5% of whom were infected by HCV genotype 4. Current alcohol use is more frequently reported in migrants from East Europe vs. others (Supplementary Table 1).

Comorbidity profile and cofactors for liver disease progression

Comorbidity profile in migrant and native patients is shown in Table 2. Autoimmune, cardiovascular, type 2 diabetes, dyslipidemias, endocrine, hematological, neurological and psychiatric disorders and tumors were more frequently reported in native compared with migrant patients ($p < 0.05$).

In patients who were treated with DAA, we found significant differences in comedication usage during and after antiviral treatment between natives and migrants: 60.9% of migrants and 45.9% of natives reported no comedication use ($p < 0.001$), whereas a higher percentage of natives compared to migrants assume more than 2 comedications (40.7% vs. 19.5%, $p < 0.001$).

The prevalence of potential factors for liver disease progression (i.e. HBsAg positivity, HIV coinfection, current alcohol abuse or surrogate markers of metabolic syndrome) after HCV eradication in the DAA treated migrants and native patients, is shown in Table 3. A significantly higher HBsAg positivity was detected in migrants compared to natives (3.1% vs. 1.2% in migrants and natives respectively, $p < 0.05$). Native patients reported a higher prevalence of potential metabolic syndrome compared to migrants (32.1% vs. 18.8% in natives and migrants respectively, $p < 0.05$). A total of 39.1% of migrants and 47.1% of native patients reported at least one of the above-mentioned factors for liver disease progression.

Table 2
Comorbidities distribution in migrant and native patients.

Comorbidities		Migrants ($N = 301$*)		Natives ($N = 10,368$*)		p*
		N.	%	N.	%	
Autoimmune	No	295	98.0	9909	95.6	< 0.05
	Yes	6	2.0	459	4.4	
Cardiovascular	No	256	85.0	6436	62.1	< 0.001
	Yes	45	15.0	3932	37.9	
Cerebrovascular	No	301	100.0	10,306	99.4	> 0.05
	Yes	0	0.0	62	0.6	
Dermatologic	No	301	100.0	10,319	99.5	> 0.05
	Yes	0	0.0	49	0.5	
Type 2 Diabetes	No	275	91.4	8896	85.8	< 0.05
	Yes	26	8.6	1472	14.2	
Dyslipidemia	No	293	97.3	9822	94.7	< 0.05
	Yes	8	2.7	546	5.3	
Endocrine	No	296	98.3	9866	95.2	< 0.05
	yes	5	1.7	502	4.8	
hematological	no	295	98.0	9840	94.9	< 0.05
	Yes	6	2.0	528	5.1	
Neurological	No	298	99.0	10,018	96.6	< 0.05
	Yes	3	1.0	350	3.4	
Psychiatric	No	294	97.7	9519	91.8	< 0.001
	Yes	7	2.3	849	8.2	
Renal	No	294	97.7	10,031	96.7	> 0.05
	Yes	7	2.3	337	3.3	
Respiratory	No	299	99.3	10,268	99.0	> 0.05
	Yes	2	0.7	100	1.0	
Tumors	No	294	97.7	9660	93.2	< 0.001
	Yes	7	2.3	708	6.8	
Others	No	259	86.0	8861	85.5	> 0.05
	Yes	42	14.0	1507	14.5	

* p value Chi-square test.

Table 3
Cofactors for liver disease progression in successfully DAA treated migrant and native patients.

	Migrants ($N = 128$)		Natives ($N = 4896$)		p*
	N.	%	N.	%	
HBsAg+	4	3.1	57	1.2	< 0.05
HIV+	6	4.7	290	5.9	> 0.05
Current alcohol use	19	14.8	740	15.1	> 0.05
Metabolic syndrome	24	18.8	1570	32.1	< 0.05
One or more cofactors	50	39.1	2304	47.1	> 0.05

* p value Chi-square test.

Discussion

In this study we evaluated data of migrants in care for chronic HCV infection, as reported by the PITER cohort. PITER has a prospective design, which consists of consecutively enrolled patients in care independently of antiviral treatment [14]. Migrants enrolled in this study are those linked to care and given the consecutive criteria in enrolment and the inclusion of clinical centers distributed all over Italy could be considered representative of migrants in care for HCV in Italy.

In the present study, migrants are younger and more frequently female compared to native patients with chronic hepatitis C infection. HCV Italian patients are also older compared to chronic infected patients diagnosed in other countries and this could be explained by different epidemiology, i.e. earlier epidemic wave of HCV infection through nosocomial infection in Italy compared to other countries, where the use of intravenous drugs is the main route of HCV transmission [17,18]. On the other side the younger age of migrants could also reflect the "healthy migrant effect" usually attributed to a self-selection process prior to migration [19].

In Italy, migrant domestic/care workers have increased drastically and according to data from the National Institute of Social Security (INPS), 87.8% of them were women in 2015 [20]. This phenomenon could explain the higher percentage of female migrants observed in this cohort, especially in migrants from East Europe.

Regarding genotype distribution, although genotype 1, and in particular subtype 1b, is prevalent in both populations, genotype 4 is more prevalent in migrants, according to the observed high prevalence of migrants originating from Egypt (18.9%), where genotype 4 accounts for more than 90% of the HCV infections [3,4]. The genotype distribution has value in the epidemiological evaluation of chronic HCV infection in different populations, including routes of transmission as well as historic and current trends of human migrations. In our study, the SVR rate of patients was similar in migrant and native patients (98% and 96%, respectively), confirming that with the availability of pangenotypic DAAs, HCV genotype has no significant role as a predictor of treatment efficacy.

HCV may cause a variety of extrahepatic manifestations which need to be considered in the clinical assessment of HCV-infected Italian and migrant patients. The higher prevalence of comorbidities in natives could reflect the older age of natives vs. migrants, but underdiagnoses or difficulties in self-reporting of comorbidities in the migrant population cannot be excluded.

According to the EASL guidelines, other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease and therapeutic choices, should be systematically investigated [12]. The presence of cofactors such as HBsAg positivity and HIV coinfection, previous and continuous alcohol abuse and the presence of metabolic syndrome are predictors of a potential liver disease progression and patients who have these cofactors should continue periodic clinical assessment independently of viral eradication. The HCV chronically infected migrants in care enrolled in PITER have a higher prevalence of HBsAg compared to natives, reflecting the HBV infection rate in the countries of origin [21]. Italy is a country with very low prevalence of HBV infection thanks to the improvement of the hygienic and socioeconomic con-

ditions and the introduction of compulsory vaccination and implemented surveillance policies [22–26], compared to other countries still lacking in effective vaccination campaigns. These data again underline testing for HBV infection with particular focus in the migrant population. All patients with chronic liver disease should be tested for HBV infection for three main reasons: a) surveillance of HBV reactivation during and after anti-HCV therapy, b) evaluation of the risk of liver disease progression despite HCV viral eradication and also c) prevention with HBV vaccination of other cohabitants and/or family members who are not immune.

Regarding HIV coinfection, native patients have a higher prevalence compared to migrant patients. Notably, we found that a total of 4741 (45.7%) of natives and 108 (35.8%) of migrants were not tested for HIV status. Native patients, for whom the HIV infection was not tested, were mainly patients older than 65 years and did not report risk factors for HIV infection. For migrant population whom are younger and with unknown risk factors, the lack of testing for HIV infection is of concern. Considering the blood born route of transmission and often the same risk factors for HCV and HIV, it is of crucial importance that HIV testing in patients with chronic HCV infection is undertaken. In the era of Highly Active Anti-Retroviral Therapy (HAART) and DAA therapies, continuous surveillance of HIV co-infection in newly and already diagnosed HCV-infected individuals, with particular focus in young aged natives and migrants, is compulsory considering the risk factors for HIV infection in recent years in Italy as well as in other European countries.

Notably, in successfully DAA treated patients about 40% of migrant and native patients reported one or more potential factors for liver disease progression. This specific finding should raise clinical awareness regarding the migrant population and their continuous follow-up after viral eradication to properly identify and address cofactors for liver disease progression, that are possibly underreported.

Study limitations

This study, based on the design of PITER cohort, focused on the already linked to care patients and those who already have had access to DAA therapy and could not give indications on the prevalence of HCV in migrant population or on different types of barriers that hinder the access of migrants to optimal health care services. The population under study is not representative of migrant population in Italy, but of migrants in care and for this reason we feel this study has an external validity only for migrant population already in care and not for the whole migrant population in Italy. In addition, a properly designed study should address the migrant populations including those legally or illegally living in Italy. Specific designed studies should focus the unlinked to care for HCV infection migrant patients, whose clinical and epidemiological profile may be different from those linked to care and herein described.

Conclusions

Although migrants have different demographics, HCV genotypes, viral coinfections and comorbidities, there are no treatment restrictions and differences in DAA efficacy rates vs. natives in Italy. It is important to properly address different comorbidities and maintain the clinical assessment in Italian and migrants with comorbidities and risk factors for liver disease progression after HCV eradication.

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Declaration of Competing Interest

None

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.03.020.

Appendix

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