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COVID-19 vaccination among cirrhotics in Italy: High coverage and effectiveness of 3 doses versus 2 in preventing breakthrough infection and hospitalization ☆

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ABSTRACT

Background and Aims: Few reports, all retrospective, have evaluated vaccine coverage against COVID-19 infection in cirrhotic subjects. No data are available for European Countries. We aimed to explore this topic and potential independent predictors of lack of vaccination.
Methods: Between January 1st and June 30th 2022, 1512 cirrhotic subjects of any etiology were consecutively enrolled in an observational - prospective study in 8 referral centers in Italy. Adjusted Odds Ratios (O.R.) for the association with lack of vaccination and with occurrence of breakthrough infection were evaluated by multiple logistic regression analysis.
Results: Overall vaccine coverage was 89.7% (80% among people born abroad). Among the 1358 vaccinated people, 178 (13.1%) had a breakthrough infection; of them 12 (6.7%) were hospitalized, but none died. Independent predictors associated with lack of vaccination were birth abroad, age <65 years and lower years of schooling. Child stage B/C was the only independent predictor of breakthrough infection. Occurrence of breakthrough infection was more likely reported in subjects who received 2 doses of vaccine than in those who received 3 doses (33.9% versus 9.0%; $P<0.001$).
Conclusion: High vaccine coverage against COVID-19 infection is observed among cirrhotic subjects in Italy. Vaccine is effective in preventing severe outcomes. Three doses are more effective than two, even in cirrhotic subjects.
Lay Summary: This large cohort study evidenced high vaccine coverage against COVID-19 infection among cirrhotic subjects in a European country and the effectiveness of vaccine in preventing severe outcomes. Three doses of vaccine are more effective than two in preventing breakthrough infection and hospitalization. Informative campaigns targeting people younger than 65 years of age and those with lower years of schooling may increase these excellent results.

1. Introduction

Subjects with liver cirrhosis, once infected with COVID-19 virus, have high rate of hospitalization, liver decompensation and death [1]. Among patients with cirrhosis, COVID-19 was associated with a 2.38-fold (95% C.I., 2.18–2.59) increased risk of a 30-day mortality,

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and among patients with COVID-19 and chronic liver disease, presence of cirrhosis was associated with a 3.31-fold (95% C.I., 2.91–3.77) risk of 30-day mortality [2]. A key point of these severe outcomes is the innate and adaptive immune dysregulation present in subjects with liver cirrhosis [3]. Another important step is played by bacterial translocation from the intestinal lumen to mesenteric lymph nodes, able to increase the level of endotoxins and cytokines [4].

Development of effective vaccines against COVID-19 has been rapid. These have been highly effective in phase 3 clinical trials, offering a 94 to 95% protection from infection [5,6]. As for the other vaccines (such as those against *Streptococcus* pneumoniae [7], influenza [8] and hepatitis B virus [9], subjects with liver cirrhosis show a suboptimal antibodies response even against COVID-19 vaccine [10] as consequence of their immune dysfunction [3].

A cohort study of US veterans with cirrhosis showed that administration of 2 doses of mRNA vaccines was associated with a 100% reduction in hospitalization and death. However, this reduced schedule had a delayed and lower (78.6%) efficacy against COVID-19 breakthrough infection [11]. A more recent survey has confirmed the strong reduction of mortality in subjects with post vaccination COVID-19 infection, among both those with either compensated (HR, 0.19: 95% C.I. 0.08–0.45) and decompensated (HR, 0.27: 95% C.I. 0.08–0.90) cirrhosis [12]. Accordingly, international liver societies guidelines (i.e. AASLD and EASL) recommend COVID-19 vaccination for subjects with chronic liver disease [13,14].

Thus, knowledge of COVID-19 vaccine coverage and characteristics of subjects unvaccinated are of paramount importance to address and improve vaccination policy.

Few and retrospective reports have explored this topic. National data from the Veterans Health Administration in US has shown that 60% of cirrhotic patients received a SARS-COVID-2 vaccination [15]. In eastern China only 37.1% of decompensated cirrhotic subjects received at least one dose of vaccination, while 62.9% remained unvaccinated despite vaccination in this population has been shown to be safe [16].

Aim of this survey was to evaluate, for the first time in a European country, vaccine coverage and potential predictors associated with lack of vaccination against COVID-19 infection in a large sample of cirrhotic subjects recruited in 8 liver units across Italy. Attention has also been addressed to the rate and predictors of breakthrough infection among subjects with completion of the primary vaccination cycle.

2. Patients and methods

2.1. Study design and patients

This is a multicentre observational study, prospectively enrolling all consecutive patients with cirrhosis of any etiology. The study was performed in 8 tertiary centers (3 in the North, 1 in the centre, 3 in the South and 1 in Sicily) during a six-month period, from January 1st to June 30th, 2022. Seven liver units and 1 infectious disease unit participated. All cirrhotic subjects, regardless of the etiology, aged 18 years or older, consecutively observed as either inpatients or outpatients, were prospectively recruited. Incident cases were defined as those who were first diagnosed with liver cirrhosis during the study period; “prevalent cases” as those observed during the study period but with an already known diagnosis of liver cirrhosis. Subjects with hepatocellular carcinoma and/or liver transplantation were excluded from the study.

Subjects were classified as being vaccinated if they reported that they had received Coronavirus vaccine in the past. Patients were classified as having post-vaccination COVID-19 if the infection was diagnosed more than 14 days after the full vaccination. Ascertainment of COVID-19 infection was determined by a protease COVID-19 polymerase chain reaction (PCR) obtained by nasal swab.

Patients were evaluated only once at their first observation. In this occasion, a questionnaire was administered to subjects. Once evaluated, subjects were no longer followed-up.

Data were collected on an anonymous form at each participating center. The questionnaire contained information on socio-demographic characteristic of subjects, etiology and stage (Child score) of liver cirrhosis, referral pattern, self-reported history of vaccination, outcomes in vaccinated subjects, and potential reasons for vaccination or not vaccination against COVID-19.

All subjects gave their written consent to participate to the study, which was carried out in conformity with the 2013 revision of the Declaration of Helsinki. The study was approved by the ethic committee of Casa Sollievo della Sofferenza Hospital – IRCCS – San Giovanni Rotondo.

2.2. Diagnostic criteria

Liver cirrhosis was based on the presence of the peculiar clinical, biochemical, ultrasound signs [17] and transient elastometry performed by Fibroscan [18]. Etiology of liver cirrhosis was based on the criteria stated in a previous published survey [19].

2.3. Serological assays

Viral hepatitis serum markers (HBsAg and HCV) were determined by commercial immune-enzymatic assays (ELISA) in the laboratories of the eight hospital participating in the survey. The kits used were: HBsAg EIA Abbott for HBsAg detection and Ortho HCV 3.0 ELISA for HCV detection.

Clinical COVID-19 infection was laboratory-confirmed by a positive result of COVID-19 PCR by nasal swab.

2.4. Statistical analysis

Differences in proportions were evaluated by the Chi-squared test. A p value <0.05 was considered to be significant.

Crude Odds Ratio (OR) and their 95% Confidence Intervals (CI) for the association of outcome variable (vaccination status) with the socio-demographic and clinical characteristics of the subjects, were calculated by univariate analysis. In order to control for the disturbing influence of confounders, the independent predictors of lack of Coronavirus vaccination were identified by multiple logistic regression analysis. In the model, lack of vaccination was the outcome variable; age, area of birth, area of residence, years of schooling, etiology and Child stage were the forced variables. For the Odds ratios estimates, the reference category for each variable was that reporting the higher vaccination coverage rate.

A further logistic regression analysis was applied only to 3 doses vaccinated people to identify characteristics of subjects independently associated with breakthrough infection. In the model occurrence of breakthrough infection was the outcome variable, while sex, age, etiology and Child stage were the forced variables.

3. Results

3.1. Main characteristic of subjects

A total of 1512 cirrhotic subjects were recruited during the 6-months enrolment period. The male to female ratio was 2.3; mean age was 64.2 years, with most cases (49.7%) being older than 64 years of age. People born abroad were 10.3%. A low rate (9.1%) of subjects were incident cases. The majority were outpatients (80.0%). Nearly three quarter of cases (74.6%) had a viral etiology. Most subjects (83.7%) had compensated cirrhosis (Child A). (Table 1).

Table 1
Baseline characteristics of 1512 subjects with liver cirrhosis. Italy, 2022.

Characteristic		N.*	%
Sex	Male	1052	69.6
	Female	460	30.4
	Sex ratio (M/F)	2.3	
Age	Mean	64.2	
	Standard Deviation	13.1	
	Median	64	
	Range	21–97	
Age distribution	≤ 50 years	201	13.3
	50–64 years	559	37.0
	≥ 65 years	750	49.7
Area of birth	Italy	1356	89.7
	Abroad	155	10.3
Area of residence	North/Center	810	53.6
	South/Islands	702	46.4
Years of schooling	≤8 years	703	46.7
	> 8 years	803	52.3
Type of case	Incident	137	9.1
	Prevalent	1374	90.9
Referral pattern	Inpatient	302	20.0
	Outpatient	1210	80.0
Etiology**	Viral	1129	74.6
	Alcoholic	253	16.8
	NAFLD/NASH	235	15.6
	Other	136	9.0
Child	A	1264	83.7
	B	190	12.6
	C	57	3.8

* For some variables, inconsistencies are due to missing values.
** Several cases had more than 1 etiological factor.

3.2. Vaccination status

In Italy, the third dose of mRNA vaccine was available for high-risk subjects since August 2021.

As many as 1358 (89.8%) subjects reported previous vaccination against COVID-19; 1137 (83.7%) of them received 3 or more doses of vaccine, 221 (16.3%) 2 doses, while none had received only one dose. Almost all (95.7%) had received RNA messenger vaccines. Among the 1358 people vaccinated, 178 (13.1%) had a breakthrough infection; 12 (6.7%) of them were hospitalised, but none died.

The mean time elapsed since the administration of the latest dose of vaccine and occurrence of breakthrough infection was 122 days (range 102–156). In the 12 subjects requiring hospitalization, the clinical presentation was respiratory distress in 9 cases, and liver decompensation in 3 cases (data not shown). Subjects who had received 2 doses of vaccine more likely reported breakthrough infection and hospitalization than those who had received 3 dose of vaccine (33.9% vs. 9.1%, $P<0.001$ and 4.6% vs. 0.5%, $P<0.001$, respectively).

Refusal of vaccination was reported by 133 (86.4%) of the 154 unvaccinated people; negative advice from the General Practitioner (G.P.s) against vaccination was reported by 10.4% of subjects. (Table 2)

Prevalence of vaccination coverage was lower in patients younger than 65 years of age (86.1% vs. 93.6%; p <0.001), in those born abroad (80.0% vs. 90.9%; p <0.001), in South Italy and Sicily residents (86.3% vs. 92.8%; $p<0.001$), in subjects with lower years of schooling (86.6% vs. 92.8%; $p<0.001$), among those with an alcoholic etiology (84.9% vs. 91.0%; $p<0.05$), and in patients with Child B/C stages (83.8% vs. 91.0%; $p<0.05$) (Table 3). Sex was the only significantly different characteristic among the 154 unvaccinated people by area of birth (54.8% in males and 45.2% in females; $p<0.05$) (Table 4).

3.3. Independent predictors of lack of vaccination

The crude O.R.s for the association of the characteristics of subjects not undergoing COVID-19 vaccination, evidenced a link with all the variables considered (age, area of birth, area of residence, years of schooling, etiology and Child stage). After adjustment by multiple logistic analysis for the confounding effect of all variables considered, age <65 years (OR = 2.88; CI 95% = 1.91–4.36), being born abroad (OR = 2.31; CI 95% = 1.43–3.75), and lower years of schooling (OR = 1.91; CI 95% = 1.25–2.92) resulted independent predictors of lack of vaccination. Area of residence, etiology and Child stage were no longer associated (Table 5).

Table 2
Vaccination status against COVID-19 of 1512 subjects with liver cirrhosis. Italy, 2022.

Characteristic		N.	%
Vaccinated	Yes	1358	89.8
	No	154	10.2
Vaccinated*	< 3 doses	221	16.3
	≥ 3 doses	1137	83.7
Type of vaccine	Adeno/vector	42	3.1
	RNA messenger	1299	95.7
	Both	17	1.3
Infection in vaccinated	Yes**	178	13.1
	No	1180	86.9
Infection by vaccination dose**	With < 3 doses	75	33.9
	With ≥ 3 doses	103	9.1
Hospitalization in vaccinated	Yes	12	6.7
	No	166	93.3
Hospitalization by vaccination	With < 3 doses	7	4.6
Dose ***/****	With ≥ 3 doses	5	0.5
Reason of vaccination	Advised by the G.P.	273	20.1
(N = 1358)	Advised by the specialist	701	51.6
	Self-reporting	384	28.3
Reason of not vaccination	Lack of information	5	3.2
(N = =154)	Refusal	133	86.4
	Advised against by the G.P.	16	10.4

* None received 1 dose of vaccine.
** $P<0.001$.
*** $P<00.1$.
**** None died.

Table 3
Prevalence of anti COVID-19 vaccination coverage in 1512 subjects with liver cirrhosis. :Italy, 2022.

Characteristic		N.vaccinated	N. subjects	%	p value Chi-square test
Sex	Male	944	1052	89.7	>0.05
	Female	414	460	90.0	
Age	< 65 years	654	760	86.1	<0.001
	≥ 65 years	702	750	93.6	
Area of birth	Italy	1233	1356	90.9	<0.001
	Abroad	124	155	80.0	
Area of residence	North/Center	752	810	92.8	<0.001
	South/Islands	606	702	86.3	
Years of schooling	≤8 years	609	703	86.6	<0.001
	> 8 years	745	803	92.8	
Etiology*	Not alcoholic	1126	1237	91.0	<0.05
	Alcoholic	112	132	84.9	
Child	A	1150	1264	91.0	<0.05
	B/C	207	247	83.8	

* 143 subjects with mixed etiology were excluded.

Table 4
Frequencies (%) of characteristics in 154 not vaccinated subjects by area of birth, Italy 2022.

Characteristic		Italians ($N = 123$)		Foreigners ($N = 31$)		p value Chi-square
		N.	%	N.	%	Test
Sex	Male	91	74.0	17	54.8	<0.05
	Female	32	26.0	14	45.2	
Age	< 65 years	82	66.7	24	77.4	>0.05
	≥ 65 years	41	33.3	7	22.6	
Etiology*	Not alcoholic	88	85.4	23	82.1	>0.05
	Alcoholic	15	14.6	5	17.9	
Child	A	92	74.8	22	71.0	>0.05
	B/C	31	25.2	9	29.0	
Reasons of not vaccination	Refusal	105	85.4	28	90.3	>0.05
	Other	19	14.6	3	9.7	

* 23 subjects with mixed etiology were excluded.

Table 5
Crude and adjusted Odds Ratios (O.R.) derived by multiple logistic regression analysis for the association of different variables with lack of anti COVID-19 vaccination in cirrhotics. Italy, 2022.

Factor		Crude O.R.	95% CI	Adjusted O.R.*	95% CI
Age	≥ 65 years	1.00		1.00	
	< 65 years	2.37	1.66 - 3.39	2.88	1.91 - 4.36
Area of birth	Italy	1.00		1.00	
	Abroad	2.51	1.62 - 3.87	2.31	1.43 - 3.75
Area of residence	North/Center	1.00		1.00	
	South/Islands	2.05	1.46 - 2.89	1.33	0.86 - 2.06
Years of schooling	>8 years	1.00		1.00	
	≤ 8 years	1.98	1.41 - 2.80	1.91	1.25 - 2.92
Etiology**	Not alcoholic	1.00		1.00	
	Alcoholic	1.81	1.08 - 3.03	1.08	0.61 - 1.90
Child	A	1.00		1.00	
	B/C	1.95	1.32 - 2.88	1.59	0.99 - 2.56

* Adjusted for the confounding effect of all listed variables.
** 143 subjects with mixed etiology were excluded.

3.4. Independent predictors of breakthrough infection

The 1137 subjects who had received 3 or more doses of vaccine were compared by occurrence of breakthrough infection. Baseline liver disease stage (i.e. Child class B/C) was the only independent predictor of this outcome (adjusted O.R. 2.30; CI 95% = 1.37–3.86). No association was found with sex, age, and etiology. (Table 6)

4. Discussion

In Italy, immunization with COVID-19 vaccine was strongly recommended for patients with chronic diseases, including those with cirrhosis, from March 2021. Thereafter, a third and a fourth dose of vaccine were recommended for these subjects since August 2021 and March 2022, respectively. Consequently, subjects enrolled in the study period (January-June 2022) may have received 3 or 4 doses of vaccine.

This is the first study assessing vaccine coverage against COVID-19 among cirrhotic subjects in a European country. The nearly 90% overall vaccine coverage is strong evidence for a very successful vaccination campaign against COVID-19 infection. Even subjects belonging to groups at lower vaccine coverage reported uptake vaccination rates from 80 to 90%. Of particular interest is the 80% rate among people born abroad, which reflects how regular immigrated have the same chance of access to our health care system as the native people in Italy do.

Table 6
Frequencies (%) of characteristics of subjects with ≥ 3 doses of COVID vaccine with or without breakthrough infection. Adjusted Odds Ratios (O.R.) derived by multiple logistic regression analysis. Italy, 2022.

Factor		With Breakthrough ($N = 103$)		Without Breakthrough ($N = 1034$)		Adjusted O.R.*	95% CI
		N.	%	N.	%		
Sex	Female	26	25.2	313	30.3	1.00	
	Male	77	74.8	721	69.7	1.25	0.76 - 2.05
Age	≥ 65 years	46	44.7	482	46.7	1.00	
	< 65 years	57	55.3	551	53.3	0.83	0.53 - 1.29
Etiology**	Not alcoholic	82	87.2	885	92.8	1.00	
	Alcoholic	12	12.8	69	7.2	1.56	0.80 - 3.07
Child	A	76	73.8	905	87.5	1.00	
	B/C	27	26.2	129	12.5	2.30	1.37 - 3.86

* Adjusted for the confounding effect of all listed variables.
** 89 subjects with mixed etiology were excluded.

The present figures largely exceed those (all from retrospective surveys) of 60% observed in USA [15] among cirrhosis of any stage, and 37.1% in China [16] among decompensated cirrhosis.

Identification of risk factors associated with unvaccinated status is critical to target interventions and further improve vaccine coverage. As in the U.S. study [15], subjects younger than 65 years of age were nearly 3-fold less likely vaccinated, reflecting an attitude of younger people to underestimate the risk of severe infection and thus defer vaccination. Even subjects with lower years of schooling are at increased risk (adj. O.R. 1.91; CI 95% = 1.25–2.92) of lack of vaccination, probably because of vaccine hesitancy stemming from personal or political beliefs. The finding that 86.4% of cases reported refusal as reason for not undergoing vaccination, further supports the previous consideration. Moreover, subjects with lower educational level may be the most at risk of falling prey to vaccine misinformation. Of notice is the observation that nearly 10% of subjects remained unvaccinated since they were not provided correct medical advice by their G.P.s, who probably did not consider vaccines against COVID-19 effective and safe for cirrhotic subjects. Thus, we suggest that counselling on the risks and benefits of COVID-19 vaccination should be specifically addressed to both cirrhotic patients and G.P.s to correct their attitude against vaccination [20]. Correct counselling will also counter the vaccine misinformation provided by some media outlets and online social media [20].

Though breakthrough infections may occur after completion of the primary vaccination cycle, these are associated with a reduced COVID-19 related hospitalization and mortality [11,12]. Our findings further strengthen the favourable effect of vaccination on severe outcomes even in cirrhotic subjects. Indeed, among the 178 subjects with breakthrough infection, only 12 (6.7%) required hospitalization and none died. Moreover, the observed better effectiveness of a third vaccine dose in preventing breakthrough infection and hospitalization, confirms the results of a recent U.S. study [21]. This latter study supports the importance of a third dose of mRNA vaccine among patients with cirrhosis, suggesting that it can also overcome their vaccine hyperresponsiveness [21].

Decompensated cirrhosis (i.e. advanced Child stage) was the only factor independently associated (adj. O.R. 2.30; CI 95% 1.37–3.86) with breakthrough infection, suggesting that liver status is the major determinant to acquire the infection in vaccinated subjects.

5. Limitations

We acknowledge some potential limitations to our study. The true proportion of breakthrough infections may be underestimated because asymptomatic infections, which more likely occur in vaccinated people [22], weren't identified. Moreover, subjects vaccinated may be less likely to receive COVID-19 PCR testing in the presence of symptoms, and thus their positive status might go undetected. However, these points may have affected the incidence rate of breakthrough infections, but not that of severe outcomes such as hospitalization and death.

6. Strength

The study is characterized by several strong points which are worth underlying. First, the observational study design, with the enrolment of all consecutive patients, generates a more accurate ascertainment than retrospective studies, generally affected by selection and ascertainment biases. Second, the large cohort (1512 cases) enrolled allows an accurate estimate of Odds Ratios for the associations explored. Third, participating centers were scattered all over the country, assuring representativeness to the observed findings. Finally, the enrolment period lasting 6 months corresponds to the interval time recommended by the Italian Association for the Study of Liver (AISF) for surveillance of cirrhotic subjects; consequently, nearly all cirrhotic subjects referring to the participating centres had the chance to be observed.

7. Conclusions

Our findings evidence very high vaccine coverage against COVID infection in Italy among patients with liver cirrhosis. Educational campaigns targeting subjects younger than 65 years of age and with lower years of schooling may further improve vaccination coverage. Patients with decompensated cirrhosis are at higher risk of breakthrough infection. Vaccine is effective in protecting against hospitalization and death. Three doses of vaccine are more effective than two in preventing breakthrough infection and hospitalization.

Conflict of interest

All authors have no conflict of interests.

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