Received: 29 December 2022 | Accepted: 19 February 2023

DOI: 10.1111/bjh.18731

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Burden of COVID-19 disease and vaccine coverages in Apulian splenectomized patients: A retrospective observational study

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Funding information
Apulia Region

Summary

Splenectomy/asplenia is a condition associated with immune-compromission and specific vaccines are recommended for these patients, including the anti-COVID-19 vaccine. Among the high-risk group for which vaccination was prioritized in Italy, the immunocompromised patients after therapies or treatments were included. The Apulian regional archive of hospital discharge forms was used to define the list of splenectomized Apulian inhabitants, considering data from 2015 through 2020. The overall vaccination status of asplenic patients was assessed via data collected from the Regional Immunization Database. The history of SARS-CoV-2 infection and the infectious disease outcomes were extracted from the Italian Institute of Health platform "Integrated surveillance of COVID-19 cases in Italy". 1219 Apulian splenectomized inhabitants were included; the incidence rate of SARS-CoV-2 infection was 15.0 per 100 persons-year with a proportion of re-infection equal to 6.4%; the proportion of hospitalization was 2.9%, with a case-fatality rate of 2.6%. The vaccine coverage (VC) for the anti-COVID-19 vaccine basal routine was 64.2%, for the first booster dose was 15.4%, and for the second booster dose was 0.6%. A multifactorial approach is needed to increase the vaccination uptake in this sub-group population and to increase the awareness of the asplenia-related risks to patients and health personnel.

KEYWORDS
asplenia, education, immunization prophylaxis, public health, SARS-CoV-2

INTRODUCTION

COVID-19, the infectious disease caused by the novel coronavirus SARS-CoV-2, was declared a pandemic in early 2020.[1] By December 7, 2022, according to the World Health Organization (WHO), confirmed cases had reached around 643 000 000, including more than 6 600 000 deaths.[2] In Italy, from February 2020 to December 2022, there have been over 24 500 000 cases and 180 000 COVID-19-related deaths (fatality rate: 0.7%).[3]

A mass vaccination campaign was started in Europe on December 27, 2020. In Italy, three high-risk priority groups were defined: healthcare workers (HCWs), the elderly (>80 years old) and patients affected by one or more comorbidities, including immunocompromised subjects after therapies or treatments,[4,5] as recommended by the Center for Disease Control and Prevention (CDC).[6] Subsequently, for these subjects, the Italian Ministry of Health recommended a third additional dose to complete the vaccine basal routine, administered at least 28 days following the last vaccine

Abbreviations: CDC, Centers for Disease Control and Prevention; GP, General Practitioner; HCW, healthcare worker; SDO, hospital discharge forms; VC, vaccine coverage.

dose.[7] Finally, a first and a second booster dose were recommended, both administered at least 120 days following the last previous dose or a confirmed Sars-CoV-2 infection.[7,8] Moreover, for frail subjects that have received a second booster dose with monovalent mRNA vaccine, the Minister of Health recommended a further booster dose with bivalent mRNA vaccine at least 120 days after the last previous dose or a confirmed Sars-CoV-2 infection.[9]

Splenectomy/asplenia is a condition associated with immunocompromission; as part of the reticulo-endothelial system and owing to its antibody production, the spleen serves essential immunological and haematological functions. Moreover, it is crucial for both the innate and adaptive immune response and plays an essential role in removing damaged blood cells from circulation.[10] Indeed, these patients have a tenfold to fiftyfold higher risk than the general population of developing overwhelming post-splenectomy infection (OPSI) caused by encapsulated bacteria such as *Streptococcus pneumoniae* (>50% of cases), *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis*;[11,12] this risk of is possibly lifelong,[13] even if it appears to be higher in the first 2 years after splenectomy.[11] The risk of viral infections in splenectomized patients is less clear.[10]

A specific immunization schedule is recommended for these patients in compliance with international vaccination guidelines;[14] the anti-COVID-19 vaccine is recommended, too.[14] The safety and effectiveness of anti-COVID-19 vaccines in this population have been investigated in several studies, showing slightly lower effectiveness compared to not immunocompromised subjects[15,16] and a safety profile comparable.[17]

At the time of the writing of this paper, only one study focused on the burden of COVID-19 on splenectomized patients,[10] while no paper focused on COVID-19 vaccination coverages in this population. In this context, this study aimed to estimate VCs for recommended COVID-19 vaccinations among splenectomized patients in Apulia (Southern Italy, roughly 4 000 000 inhabitants) and the infection, hospitalization and case-fatality rates, comparing them with those of the Apulian general population.

METHODS

This is a retrospective observational study. The study population was identified via the Apulian regional archive of hospital discharge forms (SDO), an online database containing all information on hospital and inpatient procedures in the whole region.[18] We considered all records referring to total splenectomy using the ICD11 code 41.5 (total splenectomy) and extended our search to all procedures performed from 2015 to 2020. The choice of 2015 is due to (i) current scientific evidence showed that although the risk of overwhelming post-splenectomy infection (OPSI) has been reported as potentially life-long, it is commonly accepted that the highest frequency of life-threatening infectious episodes is observed during the first 2 years;[11,13] (ii) the risk of viral infections in splenectomized patients is not well defined;[10] (iii) a preliminary analysis of our sample showed high mortality in this subgroup population, considering that 25% of the subjected splenectomized since 2015 resulted in being dead at the start of the pandemic, and overall 42% resulted in death by November 2022; indeed, estimating a case-fatality rate of 4.5 (95% CI = 4.0–5.1) × 100 persons-year and an average of 275 splenectomies per year (since 2000), the number of Apulian splenectomized subjects excluded by our analysis is estimated to be 1340 (95% CI = 969–1650). Only subjects living in Apulia were considered. The lists of deceased Apulian inhabitants (2015–2022) were checked using the Edotto platform (Exprivia) of the Apulian Health Information System[18] to define and subsequentially exclude the subjects deceased before the start of the pandemic.

The COVID-19 vaccination status of asplenic patients was assessed using the Regional Immunization Database (GIAVA)[18] and/or the Nation COVID-19 Immunization Database. Data relevant to the COVID-19 cases recorded (March 2020—November 2022) were extracted from the Italian Institute of Health platform "Integrated surveillance of COVID-19 cases in Italy". This platform, processed by the Italian Higher Institute of Health (ISS), integrates the microbiological and epidemiological data provided by all Italian regions, Autonomous Provinces, and the ISS SARS-CoV-2 national reference laboratory. All COVID-19 cases diagnosed by the regional and national reference laboratories fall within the scope of the surveillance; COVID-19 related hospitalizations and deaths are also reported.[19]

These data sources were extracted and matched using the patients' unique identification numbers (PINs). Only subjects alive on March 1, 2020, were eligible. We chose not to include foreign subjects with a temporary unique identification number in our study, considering that after splenectomy, they may have travelled back to their countries or settled in Italy, obtaining a non-temporary PIN, but we cannot trace it. Our investigation ended in November 2022.

The final dataset was created as an Excel spreadsheet that included sex, age at splenectomy, cause of splenectomy (trauma or other), diagnosis of COVID-19, COVID-19-related hospitalization or death, diagnosis of re-infection, vaccine prophylaxis (YES/NO) and the type of vaccine. An anonymized data analysis was performed using the STATA MP17 software.

Continuous variables are reported as the mean ± standard deviation and range and categorical variables as proportions. The COVID-19 incidence rate (x100 persons-year), the proportion of hospitalization, the case-fatality, rate and the proportion of re-infection were estimated; these indicators were estimated in the Apulian general population, too, using the same above-described data sources. Vaccine coverages (%) were defined as follows:

- First two doses ➔ subjects vaccinated with two doses of BNT162b2 mRNA vaccine, or two doses of mRNA –1273 vaccine, or two doses of ChAdOx1-S vaccine, or one dose of Ad26.COV2.S vaccine, or mixed schedule/subjects still

alive at the start of the vaccination campaign (January 2021)
- Basal routine ➔ subjects that received the first two doses + additional dose/subjects still alive at the start of the additional dose vaccination campaign (September 2021)
- First booster dose ➔ subjects that received the first booster dose/subjects still alive 120 days after the start of the additional dose vaccination campaign (January 2022)
- Second booster dose ➔ subjects that received the first booster dose/subjects still alive at the start of the second booster vaccination campaign (April 2022).

The chi-square or the exact Fisher tests were used to compare proportion between groups, and the long-rank test was used to compare the incidence rates between groups. The normal distribution of Skewness and kurtosis test was conducted to evaluate the normality of the continuous variables; any variable was normally distributed, and it was impossible to set a normalization model; therefore, the Wilcoxon rank sum test was performed to compare continuous variables between groups.

To analyse the determinants of the first two doses, basal routine (first two doses + additional dose), and first booster dose uptake (YES/NO), a multivariate logistic regression model was built for each outcome; sex (male vs. female), age at the start of pandemic (years), time from splenectomy to the start of pandemic (years), cause of splenectomy (trauma vs. malignancies) and a previous diagnosis of COVID-19 were used as determinants. The adjusted Odds Ratios (aORs) were calculated, as well as 95% Confidence Intervals (95% CIs). The Hosmer-Lemeshow's chi-squared test was used to evaluate the goodness-of-fit of multivariate logistic regression models.

Subsequently, a nested case–control study model was set up; to estimate the sample size, we considered the discrepancy in case fatality rate observed comparing COVID-19+ splenectomized patients (2.6%) and COVID-19+ general population (0.4%). The sample estimation was performed by the exact test, and a significance level (alpha) of 0.05 and the test power to 95% have been set. An allocation ratio of 1:7 was assessed, considering the ratio between the case fatality rate in splenectomized and the case fatality rate in the general population (2.6/0.4 = 6.5). A sample number of 2768 subjects was estimated, with 346 (12.5%) COVID-19+ splenectomized subjects (case group) and 2422 (87.5%) COVID-19 cases among the general population (control group). This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. Software G*Power 3.1 was used to calculate the sample size. The assignment to the groups has been performed by randomization, with the homogeneity of the two groups for the covariates age at the start of the pandemic and sex; randomization has been performed using the STATA MP17 software.

In order to better characterize our sample, information on chronic diseases was checked using the Edotto platform, identifying the user-fee exemption codes.[20] Eleven comorbidities were decodified: chronic lung diseases, cardiopathies, diabetes mellitus and other metabolic diseases, chronic renal failure/adrenal insufficiency, hematopathies and hemoglobinopathies, tumours, HIV and immunodepression, chronic inflammatory diseases and bowel malabsorption syndromes, chronic liver diseases, multiple pathologies and dementia. Moreover, these data were integrated with the info reported on the Italian Institute of Health platform "Integrated surveillance of COVID-19 cases in Italy" and on the archive of hospital discharge forms.

Finally, to analyse the determinants of COVID-19-related hospitalization and death, a multivariate logistic regression model was built for each outcome; the group variable (splenectomized vs. general population) was considered as the main determinant, adjusted for sex (male vs. female), age at the start of pandemic (years), the number of comorbidities and COVID-19 vaccine basal routine (as defined per subgroup population). These models were repeated considering only subjects aged 65+ years. The aORs were calculated, as well as 95% CIs. The Hosmer-Lemeshow's chi-squared test was used to evaluate the goodness-of-fit of multivariate logistic regression models.

A two-sided p-value<0.05 was considered an indicator of statistical significance for all tests.

RESULTS

Since 2015, 1650 subjects living in Apulia have undergone splenectomy; 1227 of them (74.4%) were still alive on March 1, 2020, but 8 (0.7%) of them had a temporary PIN and therefore were excluded. 718 of 1219 enrolled patients (58.9%) were male; the mean age at splenectomy was 52.4 ± 20.8 years (range: 4–95), and the average age at the start of the COVID-19 pandemic was 55.3 ± 20.6 years (range: 7–100). 517 out of 1219 splenectomies (42.4%) were required due to traumatic injuries; demographic characteristics of our sample, per cause of splenectomy, are reported in Table S1.

The incidence rate of SARS-CoV-2 infection was 15.0 per 100 persons-year (n = 346) with a proportion of re-infection equal to 6.4% (n = 22); Figure 1 describes the trend of confirmed cases since March 2020. The proportion of hospitalization was 2.9% (n = 10), with a case-fatality rate of 2.6% (n = 9). No hospitalization or death was associated with the second infection. No difference in these outcomes was evidenced considering the cause of splenectomy (Table S1). The characteristic of hospitalized and dead patients are reported in Table S2.

Table 1 describes the above-reported rates and indicators of disease per age class, comparing them with the equivalent indicators in the Apulian general population; demographic characteristics of the Apulian general population are reported in Table S3.

The vaccine coverage for anti-COVID-19 first two doses was 87.6% (n = 993 of 1133 still alive at the start of the vaccination campaign, considering both COVID-19- related

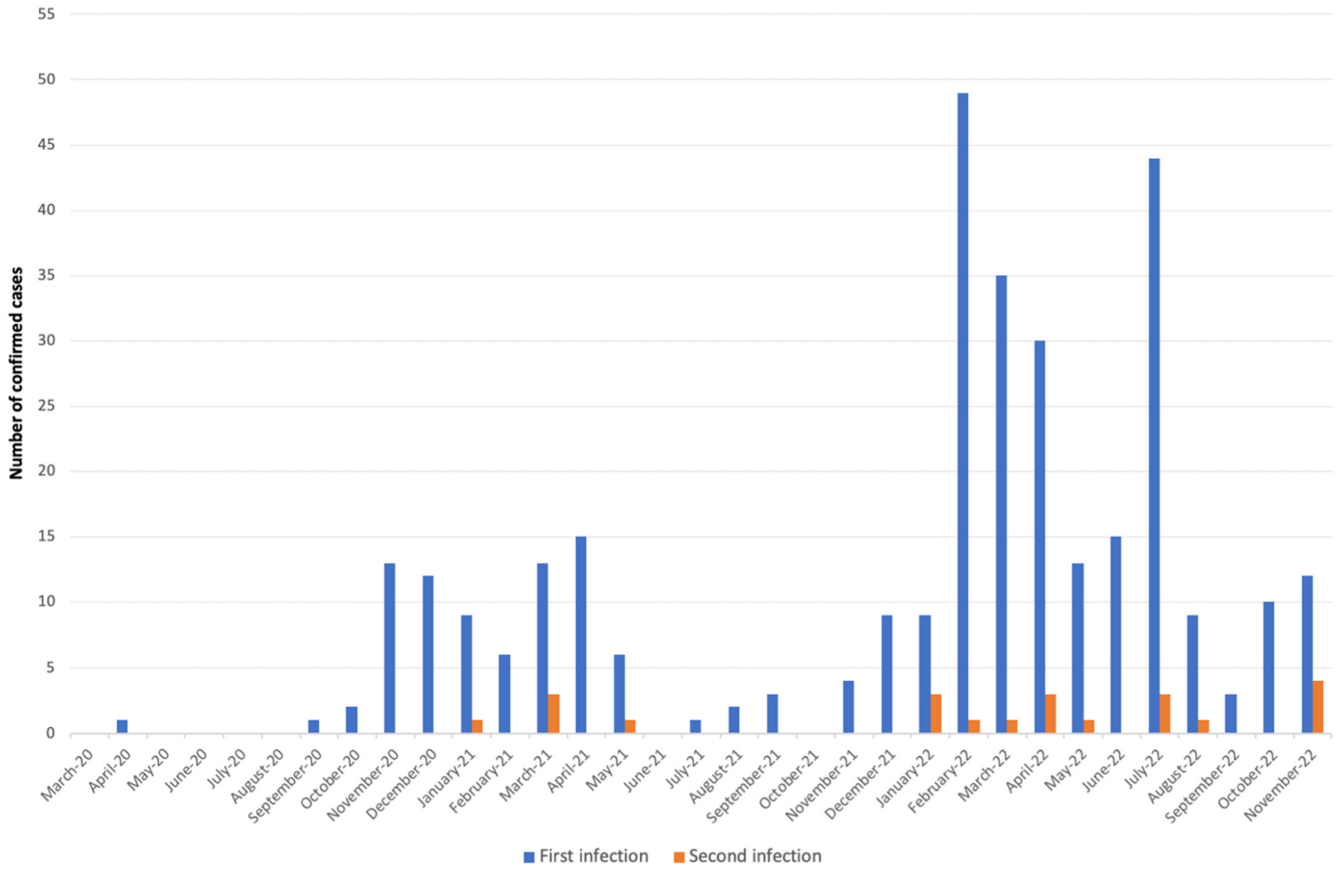

FIGURE 1 Trend of SARS-CoV-2 infection confirmed cases among splenectomized patients.

and not related deaths); most of them (n = 741; 77.6%) have been vaccinated with BNT162b2 mRNA vaccine, followed by vaccinated with mRNA-1273 vaccine (n = 151; 15.8%), ChAdOx1-S vaccine (n = 51; 5.3%) and Ad26.COV2.S vaccine (n = 12; 1.3%). Considering that Italian Public Health institutions recommended an additional dose for these immunocompromised subjects,[7] the vaccine coverage for the full basal cycle (vaccine basal routine + additional dose) dose was 64.2% (672 of 1089 subjects still alive at the start of additional dose vaccination campaign); for 414 of them (68.3%), the administered addition dose was BNT162b2 mRNA vaccine, and for 192 (31.7%) it was mRNA-1273 vaccine. The vaccine coverage for the first booster dose was 15.4% (161 of 1049 subjects still alive at least 120 days after the start of the first booster vaccination campaign); 154 of them (95.7%) have been vaccinated with the BNT162b2 mRNA vaccine, and 7 (4.3%) with mRNA-1273 vaccine. Only 0.6% (n = 6 of 956 still alive at the start of the second booster vaccination campaign) of them received the second booster dose.

Table 2 describes the vaccine coverages per age class, comparing them with the equivalent values in the Apulian general population. The multivariate analyses of vaccine uptake are described in Table 3.

The characteristics of subjects included in the nested case–control study are reported in Table S4. The multivariate analyses of the determinants of COVID-19-related hospitalization and death are described in Table 4.

CONCLUSIONS

The results of our study highlighted that splenectomy was not associated with an increased risk of COVID-19 infection and re-infection; this is also confirmed by our case/control sub-analysis, which did not evidence a statistically significant difference in infection and re-infection between groups. On the other hand, the proportion of hospitalization and the case fatality rate were significantly higher compared to the ones of the Apulian general population (2.9% vs. 0.5% and 2.6% vs. 0.4%, respectively), especially considering >64 years old subjects. The higher risk of COVID-19-related hospitalizations and death in splenectomized patients is confirmed in the multivariate regression analysis performed in the context of the case/control study, both for all ages (aOR = 3.23; 95% CI = 1.11–9.38 and aOR = 5.82; 95% CI = 1.24–27.39, respectively) and 65+ years old subjects (aOR = 3.00; 95% CI = 0.85–10.54 and aOR = 5.83; 95% CI = 1.24–27.51, respectively). In the light of our regression models, asplenia/hyposplenia may be associated with increased susceptibility to complications of SARS-CoV-2 infection; nevertheless, more research is needed to strengthen this evidence. These

TABLE 1 Infection rates, proportion of hospitalization, case-fatality rate and proportion of re-infection in Apulian splenectomized vs. general population, per age class.

	Splenectomized				General population				*p*-value			
Age class	Incidence rate (x100 persons-year)	Proportion of hospitalization	Case-fatality rate	Proportion of re-infection	Incidence rate (x100 persons-year)	Proportion of hospitalization	Case-fatality rate	Proportion of re-infection	Incidence rate (x100 persons-year)	Proportion of hospitalization	Case-fatality rate	Proportion of re-infection
0–17	21.1	0.0%	0.0%	6.7%	22.4	0.0%	0.0%	5.8%	0.850	-	-	0.815
18–49	16.6	0.0%	0.0%	8.9%	15.1	0.1%	0.0%	6.4%	0.360	-	-	0.038
50–64	15.6	1.2%	0.0%	7.2%	14.2	0.3%	0.1%	5,1%	0.500	0.006	0.595	0.108
65–79	12.4	5.1%	5.1%	2.5%	12.7	1.3%	0.9%	3.3%	0.867	<0.0001	<0.0001	0.404
80+	12.6	14.7%	14.7%	2.9%	9.2	4.3%	3.8%	3.3%	0.163	<0.0001	<0.0001	0.576
Total	15.0	2.9%	2.6%	6.4%	15.0	0.5%	0.4%	5.4%	1.000	<0.0001	<0.0001	0.123

results are comparable to the ones of a 2021 Danish study;[10] the authors conducted a case–control study of all individuals with a diagnosis COVID-19 in Denmark through December 31, 2020, examining the association between previous splenectomy and the risk of COVID-19 infection, hospitalization and death. They matched 165623 subjects with COVID-19 diagnosis with 493 300 controls; 130 and 422 splenectomies were performed in the cases and controls, respectively, concluding that splenectomized patients did not have a higher risk of COVID-19 infection than non-splenectomized subjects (aOR = 0.89; 95% CI = 0.73–1.08), but they may have an increased risk of hospitalization or death (aOR = 1.44; 95% CI = 0.79–2.61).[10] Anyway, our regression models showed that the greater risk of hospitalization or death could not be explained only by the condition of asplenia, but it must be considered that the increasing age seems to be one of the main determinants of complications of COVID-19; on the other hand, COVID-19 vaccination is a solid protective factor to prevent hospitalizations and deaths; several studies confirmed younger age and COVID-19 vaccination as protective determinants of COVID-19 fatal outcomes in high-risk patients.[21–24]

Considering the vaccination status, higher vaccination coverage for basal routine is found in splenectomized patients; nevertheless, for these patients, an additional dose is recommended, considering their immunocompromising status;[7] therefore, the comparison of the VC for basal routine in splenectomized patients with the VC for basal routine in the general population is very critical (62% vs. 80%, respectively). One reason for this discrepancy is that this type of patient is often not recognized by vaccine health professionals or family doctors, or branch specialists as being at greater infectious risk, as confirmed by the literature;[11] the on-field experience tells us that without a careful anamnestic collection, these patients can omit to have undergone a splenectomy operation, as presumably after the operation they have not been sufficiently educated about their immunocompromised condition. Therefore, in a large proportion of patients, the additional dose could have been interpreted as a first booster dose and the first booster dose as a second booster dose. Indeed, a 2019 Italian study[25] reported that vaccination prophylaxis should be an opportunity to raise patients' awareness regarding their susceptibility to infections. The authors evaluated the effectiveness of an active recall protocol for performing influenza vaccination in the years following splenectomy among 96 patients splenectomized at the Bari Policlinico University General-Hospital, and taken care of after surgery by the Hygiene Unit; at the end of the 2017/18 influenza season, 73 (76%) of patients reported having received the flu shot, without differences between groups (active recall group = 80% vs. control group = 72%; *p*-value = 0.330), concluding that effective communication at the time of the vaccine counselling after splenectomy is related to good adherence to the vaccination program even after several years. Moreover, a specific policy of active recall for these patients had not been implemented by Apulia Public Health Institutions, and the promotion of vaccination

TABLE 2 Anti-COVID-19 vaccine coverages in Apulian splenectomized vs. general population, per age class.

	Splenectomized				General population		
Age class	First two doses	Basal routine (first two doses + additional dose)	First booster	Second booster	Basal routine	First booster	Second booster
5–17	67.6%	40.5%	0.0%	0.0%	56.0%	19.2%	0.1%
18–49	85.3%	60.0%	2.7%	0.3%	75.0%	49.5%	0.9%
50–64	91.8%	64.2%	16.6%	1.3%	88.0%	56.5%	5.3%
65–79	88.8%	63.8%	32.1%	0.9%	92.3%	61.8%	19.3%
80+	89.1%	64.2%	26.4%	0.0%	96.1%	60.4%	29.1%
Total	87.6%	61.7%	15.4%	0.6%	80.1%	50.2%	7.0%

TABLE 3 Multivariate logistic regression models of vaccine uptake.

	First two doses		Basal routine		First booster	
Determinant	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value	aOR (95% CI)	*p*-value
Age (years)	1.01 (1.01–1.02)	0.011	1.00 (0.99–1.01)	0.173	1.05 (1.04–1.06)	<0.0001
Sex (male vs. female)	0.62 (0.42–0.93)	0.019	1.09 (0.84–1.41)	0.309	0.90 (0.62–1.30)	0.558
Time from surgery to the start of the pandemic (years)	1.15 (1.03–1.27)	0.011	1.08 (1.01–1.16)	0.033	0.97 (0.87–1.07)	0.502
Cause of splenectomy (trauma vs. hematopathies)	0.91 (0.61–1.36)	0.651	0.72 (0.55–0.95)	0.020	0.59 (0.39–0.89)	0.013
Diagnosis of COVID-19 before vaccination	0.55 (0.29–1.06)	0.075	2.22 (1.22–4.03)	0.009	2.94 (1.63–5.33)	<0.0001
	Goodness-of-fit *p*-value = 0.599		Goodness-of-fit *p*-value = 0.779		Goodness-of-fit *p*-value = 0.439	

was left to national and regional communication campaigns targeted at the chronic patient; therefore, the prophylaxis in this sub-group population has been left to the competence of General Practitioners and Health Prevention Departments.

In light of the increased risk of hospitalization and death in this age group, this figure appears serious, considering that vaccination has shown remarkable effectiveness in preventing serious complications and death in this population subgroup.[15,16] Moreover, another critical issue was found in patients over 80 years old, where vaccination coverage is slightly lower than in the general population, considering the first two doses (89% vs. 96%). Functional and anatomical asplenia increase susceptibility to infectious diseases, especially in the elderly.[26,27] Low VCs are probably related to a misperception of risk by general practitioners and/or specialized branch physicians. These professionals may identify possible adverse events following immunization as critical risks for vulnerable patients, for whom infections are significantly worse in terms of morbidity and mortality.[26]

Multivariate regression models investigated the main determinants of vaccination uptake in splenectomized subjects, showing that older subjects, females, a longer time since the splenectomy, and a previous diagnosis of COVID-19 were associated with a better uptake. Of particular interest was the evidence that for basal routine and first booster dose, a diagnosis of malignancy is associated with a better uptake (as confirmed by the analysis reported in Table S1). The on-field experience teaches us that splenectomized subject due to trauma is often not aware of his/her condition and the risk associated with asplenia, and, therefore, these subjects may underestimate the risks of COVID-19 complications; on the other hand, the presence of an underlying chronic condition can increase awareness of the risk both by the patient and by their doctor, thus obtaining better vaccination compliance.

The strengths of our study are the long study period (3 years), the large population we addressed and the comparison with the Apulian general population; to our knowledge, only one study in the scientific literature investigated this phenomenon,[10] focusing only of the burden of disease, and did not investigate the immunization status. Moreover, we estimated this subgroup population's risk of COVID-19-related hospitalization and death. The major limitation is that some of our data sources (i.e., Edotto platform) are built for administrative and non-epidemiological purposes, so there is a theoretical risk of bias. On the other hand, we could not evaluate the correlation between VCs and community care determinants. Furthermore, if some splenectomized patients had moved abroad after the operation, we would have no way of estimating the outcomes in our analysis; this risk is low, therefore it does not appear to be a critical bias. Another limitation is that the proportion of splenectomized patients who were advised to shield is

TABLE 4 Multivariate logistic regression models of COVID-19-related hospitalizations and deaths.

	Total sample				65+ years old subjects			
	Hospitalization		Death		Hospitalization		Death	
Determinant	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Group variable (splenectomized vs. general population)	3.23 (1.11–9.38)	0.031	5.82 (1.24–27.39)	0.026	3.00 (0.85–10.54)	0.088	5.83 (1.24–27.51)	0.026
Age (years)	1.09 (1.05–1.13)	<0.0001	1.17 (1.08–1.29)	<0.0001	1.15 (1.07–1.24)	<0.0001	1.13 (1.03–1.24)	0.007
Sex (male vs. female)	0.98 (0.41–2.36)	0.965	1.36 (0.38–4.86)	0.638	0.99 (0.35–2.74)	0.989	1.42 (0.40–5.04)	0.591
Comorbidities								
1 vs. none	1.35 (0.42–4.33)	0.610	0.38 (0.06–2.19)	0.276	1.25 (0.32–4.94)	0.751	0.40 (0.07–2.29)	0.302
≥2 vs. none	0.92 (0.28–3.01)	0.895	0.35 (0.07–1.72)	0.198	0.70 (0.18–2.68)	0.600	0.36 (0.08–1.72)	0.201
Basal vaccination routine	0.32 (0.11–0.90)	0.030	0.08 (0.02–0.40)	0.002	0.17 (0.05–0.58)	0.004	0.09 (0.02–0.42)	0.002
	Goodness-of-fit p-value = 0.181		Goodness-of-fit p-value = 0.997		Goodness-of-fit p-value = 0.923		Goodness-of-fit p-value = 0.623	

not known. Finally, the choice of the study cohort (2015–2020) may be contested; in the light of the considerations reported in the method paragraph, we believe that the evaluation starting from the 2015 cohort was sufficient to make the data relating to infection and vaccination coverage representative for the entire population of Apulian at high-risk splenectomized patients. Future studies should focus on the effectiveness and long-term immunogenicity of COVID-19 vaccination, the serological response to the immunization, and the adverse events following immunization in splenectomized subjects.

A multifactorial approach should be implemented to achieve high vaccination coverage in this population. The introduction of intra-hospital vaccination protocols for chronic patients has been shown to enormously increase the VC (up to 10-fold) of these individuals.[28] When it is impossible to vaccinate in a hospital setting, cooperation between the vaccinologist, branch specialist, and General Practitioner (GP) is a determining element for achieving high vaccination rates in these subjects. Currently, the lack of recommendations by healthcare workers, especially GPs and branch specialists, is considered the main barrier to immunization. A 2021 review identified the lack of skilled HCWs in vaccinology and the unsatisfactory information available for patients as two of the major determinants of low vaccination compliance.[11] The training of healthcare personnel might consist of specific courses, workshops and events designed explicitly for HCWs involved in managing the asplenic patient (surgeons, vaccinologists, GPs). At the same time, educating patients about their health conditions and the associated risks is crucial to raising awareness of risks among patients and parents/caregivers.[29] Efficient communication by public health institutions is required; indeed, at the start of the vaccination campaign, the Italian Ministry of Health specified among the subjects at higher risk those immunocompromised subjects after therapies or treatments,[4] while for further doses, a more generic "immunocompromission" and/or "hemopathies" voices were reported.[7,8] This change may have confused patients and healthcare professionals.

In conclusion, VCs in Apulian splenectomized patients are unsatisfactory, especially considering the booster doses. This is a significant issue, considering that the highest risk of hospitalization and death is reported in this sub-group, compared to the general population. Public health institutions need to enforce new strategies aimed at increasing vaccination attitudes in this population, implementing educational actions for patients and parents/caregivers, training for GPs and specialists, and effective communication promotions.

AUTHOR CONTRIBUTIONS

Francesco Paolo Bianchi and Silvio Tafuri conceived and led the study. Donato Rizzi, Noemi Signorile and Eustachio Cuscianna conducted database building, extraction and coding. Francesco Paolo Bianchi and Donato Rizzi queried and analysed the data. Francesco Paolo Bianchi and

Pasquale Stefanizzi codrafted the first version of the article. Giovanni Migliore and Antonio Daleno supervised the study. All authors made a substantial intellectual contribution to the study, interpreted the data, discussed the results and reviewed, edited and approved the final version of the manuscript.

ACKNOWLEDGEMENT

Open Access Funding provided by Universita degli Studi di Bari Aldo Moro within the CRUI-CARE Agreement.

FUNDING INFORMATION

Research was funded by Apulia Region.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests. The manuscript has not been previously presented in any meeting.

DATA AVAILABILITY STATEMENT

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bianchi FP, Stefanizzi P, Rizzi D, Signorile N, Cuscianna E, Daleno A, et al. Burden of COVID-19 disease and vaccine coverages in Apulian splenectomized patients: A retrospective observational study. Br J Haematol. 2023;201(6):1072–1080. https://doi.org/10.1111/bjh.18731