Prevalence, incidence and clinical features of SARS-CoV-2 infection in adult coeliac patients

Annalisa Schiepatti[a], Eleonora Alimenti[a], Stiliano Maimaris[a], Maria Luisa Nicolardi[a], Francesca Manzella La Barbera[a], Paola Baiardi[b] and Federico Biagi[a]

Objectives Data on SARS-CoV-2 disease (COVID-19) in adult coeliac disease (CD) are lacking. The aim of the present study is to evaluate the epidemiology and clinical features of COVID-19 in adult coeliac patients regularly followed-up at our centre since January 2015.
Methods Data about general health status and clinical features of laboratory-confirmed COVID-19 were prospectively collected over the phone. Data about CD were retrospectively collected from clinical notes. Prevalence and incidence of COVID-19 were compared between the coeliac cohort and the figures in the general population of Lombardy, Northern Italy between 20 February to 5 June 2020 provided by the Italian National Institute of Health (Istituto Superiore di Sanità) and the Lombardy regional government.
Results Nine out of 324 patients contracted COVID-19, thus resulting in a prevalence of 2.78% [95% confidence interval (CI) 0.98–4.58] and an incidence rate of 8.15/1000 person-month (95% CI 4.24–15.66). Prevalence of COVID-19 ascertained by means of nasal swab was 1.79% (95% CI 0.22–3.35) and the incidence rate 5.26/1000 person-month (95% CI 2.19–12.63), without difference from the general population. Clinical type of CD, age, sex, duration and adherence to a gluten-free diet, and mucosal healing did not differ between coeliac patients with and without COVID-19. None of the 9 patients with COVID-19 required hospitalization.
Conclusion Patients with CD do not seem to carry an increased risk of COVID-19 compared to the general population and their disease course is mild. Eur J Gastroenterol Hepatol 33: 1361–1366

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the ongoing COVID-19 pandemic which originated in Wuhan, China in December 2019 [1]. Currently, the Lombardy region, Northern Italy has been one of the most severely hit regions by this crisis worldwide. Infection by SARS-CoV-2 is characterized by a variety of clinical syndromes, ranging significantly in severity from asymptomatic infection, flu-like symptoms, pneumonia, up to acute respiratory distress syndrome [2–4]. Several clinical and demographic factors have been described as predisposing for COVID-19 morbidity and mortality, including increasing age, male sex, ethnicity and comorbidities such as diabetes, hypertension, cardiovascular disease, chronic respiratory disease, and cancer [2,3].

Coeliac disease (CD) is a common chronic gluten-dependent enteropathy characterized by an heterogeneous clinical picture and an increased morbidity and mortality mainly due to its complications [5–8]. These include rare premalignant and malignant conditions such as refractory CD (RCD), enteropathy associated T-cell lymphoma, abdominal B-cell lymphomas and small-bowel carcinoma [8]. Patients with complicated CD may be at increased risk of contracting infections because of severe malnutrition, treatment with immunosuppressive drugs or chemotherapy [2,3,8,9]. Apart from this specific subgroup of coeliac patients, overall an increased risk of both bacterial and viral infections has been reported in CD. This is the case for pneumococcal pneumonia [10,11], sepsis [12], *Clostridium difficile* infection [13], tuberculosis [14], herpes zoster [15] and complications from influenza virus [16,17]. Indeed, there are theoretical concerns related to the fact that risk of infections persists in the long-term, even after the adoption of a gluten-free diet (GFD), which is currently the mainstay for treatment of CD [15–17].

As urged by the major patients' societies for CD worldwide [18–22], there is a need for data on risk of COVID-19 in CD. This represents a crucial issue for clinical practice of different medical specialists given the frequency of CD in the general population and the interest of patients affected by such a chronic disease to know about their own risk of contracting the infection. To our knowledge, no studies investigating the epidemiology and clinical features of COVID-19 in CD have been published so far.

The aim of the present study is two-fold: i) to describe the epidemiology, clinical features and outcomes of COVID-19 in a group of adult coeliac patients who have been regularly followed-up at our centre in Pavia, Lombardy, Northern Italy since 2015; ii) to compare incidence and prevalence of COVID-19 in our cohort of coeliac patients with the figures in the general population of Lombardy region, Northern Italy in the period between 20 February and 5 June 2020.

European Journal of Gastroenterology & Hepatology 2021, 33:1361–1366
Keywords: coeliac disease, COVID-19, epidemiology, SARS-CoV-2
[a]Istituti Clinici Scientifici Maugeri, IRCCS, Gastroenterology Unit of Pavia Institute, University of Pavia and [b]Direzione Scientifica Centrale, Fondazione S. Maugeri, IRCCS, Pavia, Italy
Received 2 September 2020 **Accepted** 29 September 2020

Patients and methods

Study population and setting

This is a longitudinal single-centre study with combined retrospective and prospective design evaluating the epidemiology of COVID-19 in adult patients (aged > 18 years) affected by different forms of biopsy-proven CD. This means that patients affected by conventional seropositive CD, potential CD (PCD), seronegative CD (SNCD) and RCD have been included. Coeliac patients enrolled in the study have been regularly followed-up at the Gastroenterology outpatient clinic of IRCCS Pavia, ICS Maugeri, Pavia, Northern Italy, from January 2015 to 20 February 2020, when the local epidemic began [23,24].

Enrolment criteria

Three main groups of patients were identified in this study.

The first group is represented by coeliac patients who developed COVID-19 in the period between 20 February and 5 June 2020. Diagnosis of SARS-CoV-2 infection was based on at least one of the following two criteria: (1) a positive test result from real-time reverse transcription PCR testing for SARS-CoV-2 on a nasopharyngeal swab; (2) positive IgM or IgG specific serology for SARS-CoV-2.

The second group includes patients who developed symptoms possibly related to COVID-19 but who were not promptly and adequately investigated. In these patients, SARS-CoV-2 was neither confirmed nor excluded and they were included in the COVID-19 like group.

Finally, coeliac patients who did not develop symptoms suggestive of COVID-19 over the same period were considered as controls.

Diagnostic criteria for coeliac disease

Diagnosis of conventional CD was based on positive IgA tissue transglutaminase (tTG)/endomysial antibodies (EmA) and a certain degree of villous atrophy (≥Marsh 3a/Corazza-Villanacci B) on correctly oriented duodenal biopsy in accordance with major international guidelines [5,6]. EmA were detected on monkey oesophagus/jejunum sections using an indirect immunofluorescence kit (INOVA Diagnostic, San Diego, California, USA). We do not routinely test for tTG as in our experience both sensitivity and specificity of EmA and tTG are very similar [25]. For patients affected by total IgA deficiency, class IgG EmA/tTG were tested [5,6].

Diagnosis of PCD was made in patients with positive IgA EmA and architecturally normal duodenal biopsies [26]. VA responding to a GFD together with negative IgA EmA/tTG and exclusion of other rare causes of seronegative VA allowed the diagnosis of SNCD. HLA-DQ2/DQ8 genotype supported the diagnosis of SNCD [27]. Complications of CD were diagnosed as previously described [8].

Data collection

Between 15 May 2020 and 7 June 2020 data about general health status, type and duration of symptoms possibly related to COVID-19 occurring in the period between 20 February and 5 June 2020 were prospectively obtained by means of a phone interview [2], after collection of consent to participate in the study by each patient.

For patients with laboratory-confirmed COVID-19 data on the necessity for hospital admission, mechanical ventilation, specific treatments undergone and clinical outcomes of COVID-19 were collected. We also asked all the patients to inform us in case of development of new symptoms in the weeks ahead our contact.

For all patients, demographic and clinical data about CD were retrospectively collected from their clinical notes. These include sex, Italian region of residence, age at diagnosis of CD, clinical type of CD according to Oslo definitions (classical; non-classical; silent) [6], duration of and compliance to a GFD [28], results of follow-up duodenal biopsy, and presence of any known complications of CD prior to enrolment in the study.

Data about SARS-CoV-2 infection detected by means of nasal swab in the general population of the Lombardy region in the period between 20 February and 5 June 2020 were obtained from national reports published by the Italian National Institute of Health (Istituto Superiore di Sanità) and the Lombardy regional government [23,24]. These data were used to calculate prevalence and incidence of COVID-19 in Lombardy.

Ethics

The study was approved by the ethical review board of IRCCS Pavia, ICS Maugeri, Pavia, Italy (protocol number 2541 CE). Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (sixth revision, 2008) as reflected in a priori approval by the institution's human research committee.

Statistics

The prevalence and the incidence of COVID-19 in the coeliac cohort and the Lombardy region were reported together with their 95% exact binomial confidence interval (CI). Data on clinical features of CD and COVID-19 were summarized as counts and percentage if categorical and as mean and SD/median and 25th–75th percentiles if continuous and normally/not normally distributed. Categorical data were compared among groups using Fisher's exact test, meanwhile, continuous variables were compared using Kruskal–Wallis one-way analysis of variance. A two-sided *P*-value less than 0.05 was considered statistically significant. Stata 12 (StataCorp, College Station, Texas, USA) was used for computation.

Results

Between 12 January 2015 and 20 February 2020, 372 coeliac patients attended our gastroenterology outpatient clinic for routine follow-up. We succeeded in contacting over the phone 324 of them, who, therefore, were included in the present study. Demographic and clinical features of these 324 patients are summarized in Table 1. No significant differences were observed between included and excluded patients, except for median age at diagnosis (higher in included patients, 32 vs. 25 years, $P = 0.03$) and duration of a GFD (lower in included patients, 92 vs. 117.5 months, $P = 0.04$).

Table 1. Demographic and clinical characteristics of patients enrolled in the study

Characteristic	All patients (N = 324)	COVID (N = 9)	Healthy (N = 271)	COVID-like (N = 44)	Global (*P*-value)[a]	COVID vs. healthy (*P*-value)[a]	COVID vs. COVID-like (*P*-value)[a]	COVID-like vs. healthy (*P*-value)[a]
Female sex	234 (72%)	7 (78%)	194 (72%)	33 (75%)	0.92	1.00	1.00	0.72
Age at diagnosis of CD (years)	31 ± 17	27 ± 13	33 ± 17	29 ± 19	0.35	0.29	0.69	0.29
Age at enrolment (years)	41 ± 15	35 ± 12	42 ± 16	41 ± 17	0.35	0.18	0.45	0.47
Test for SARS-CoV-2	24 (7%)	9 (100%)	11 (4%)	4 (9%)	<0.001	<0.001	<0.001	0.14
Patients living in Lombardy	280 (86%)	9 (100%)	232 (86%)	39 (89%)	0.44	0.61	0.57	0.81
Final diagnosis					0.91	1.00	1.00	1.00
Coeliac disease	297 (92%)	9 (100%)	247 (91%)	41 (93%)				
Potential coeliac disease	20 (6%)	0	17 (6%)	3 (7%)				
Refractory coeliac disease	4 (1%)	0	4 (1.5%)	0				
Seronegative CD	3 (1%)	0	3 (1.5%)	0				
Oslo type of CD [6]					0.12	0.07	0.1	0.63
Classical	203 (63%)	3 (33%)	171 (63%)	29 (66%)				
Non classical	95 (29%)	6 (67%)	76 (28%)	13 (29%)				
Silent	26 (8%)	0	24 (9%)	2 (5%)				
Follow up biopsy					0.65	1.00	1.00	0.46
Not performed	130 (40%)	4 (44%)	105 (39%)	21 (48%)				
Persistence of VA (>Marsh 3a)	7 (2%)	0	7 (2%)	0				
Resolution of VA (Marsh 0–2)	187 (58%)	5 (56%)	159 (59%)	23 (52%)				
Adherence to a GFD [28]					0.78	1.00	1.00	0.33
Adherent	306 (95%)	9 (100%)	257 (95%)	40 (91%)	0.31	0.79	0.45	0.13
Not adherent	10 (3%)	0	8 (3%)	2(4.5%)				
Not evaluable/available	8 (2%)	0	6 (2%)	2 (4.5%)				
Time on a GFD, months (IQR)	95 (50.5–182)	95 (36–179)	86 (44–179)	113.5 (70–197.5)				
Death	1 (0.3%)	0	0	1 (2.3%)	0.16	-	1.00	0.14

Values are expressed in number (%), median (IQR) or mean ± SD.
CD, coeliac disease; GFD, gluten-free diet; IQR, interquartile range; VA, villous atrophy.
[a]Categorical data were compared among groups using Fisher's exact test, meanwhile continuous variables were compared using Kruskal–Wallis one-way analysis of variance. *P*-values less than 0.05 are significant.

Table 2. Prevalence and incidence of COVID-19 in coeliac patients compared to the general population of Lombardy region

Studied population	Prevalence (95% CI)	*P*-value (Fisher's exact)	Incidence/1000 PM (95% CI)	*P*-value (Fisher's exact)	OR (95% CI)
COVID-19 in all coeliac patients	2.78% (95% CI 0.98–4.58%)	-	8.15 (4.24–15.66)	-	-
COVID-19 in coeliac patients residing in Lombardy	3.21% (95% CI 1.14–5.29%)	-	9.46 (4.92–18.18)	-	-
COVID-19 diagnosed by nasal swab in coeliac patients residing in Lombardy	1.79% (95% CI 0.22–3.35)	0.11	5.26 (2.19–12.63)	0.10	2.00 (0.84–4.84), P = 0.12
COVID-19 diagnosed by nasal swab in the general Lombardy population[a]	0.90 % (95% CI 0.89–0.90)		2.57 (2.56–2.59)		

[a]Prevalence and incidence were calculated from data provided by the Italian National Institute of Health (Istituto Superiore di Sanità) and the Lombardy regional government [18,19]. As of 5 June 2020, cases of COVID-19 ascertained by nasal swab in Lombardy were 90 633 and the population of Lombardy was 10 060 574. 95% CI, 95% confidence interval; OR, odds ratio; PM, person-months.

Prevalence and incidence of COVID-19 in coeliac patients

Fifty-three patients (16%) developed symptoms compatible with COVID-19 and 13 of them were tested for SARS-CoV-2 infection by either nasal swab or serology. Nine of these 13 patients were positive and the other 4 were negative. Among the asymptomatic patients only 11 were tested (4%), of whom all were negative.

Prevalence of laboratory-confirmed COVID-19 (nasal swab, serology) in our cohort is therefore 9/324 = 2.78% (95% CI 0.98–4.58), with an incidence rate of 8.15/1000 person-month (95% CI 4.24–15.66). No significant difference was found when patients residing outside Lombardy were excluded from the computation (prevalence: 9/280 = 3.21%, 95% CI 1.14–5.29; incidence: 9.46/1000 person-month, 95% CI 4.92–18.18). When only patients with COVID-19 ascertained by means of nasal swab were considered, prevalence was 1.79% (95% CI 0.22–3.35) and incidence was 5.26/1000 person-month (95% CI 2.19–12.63) among patients residing in Lombardy.

As of 5 June 2020, prevalence and incidence of COVID-19 ascertained by nasal swab in the Lombardy region were 0.90% (95% CI 0.89–0.90) and 2.57/1000 person-month (95% CI 2.56–2.59), respectively. Even though prevalence and incidence of COVID-19 ascertained by nasal swab in coeliac patients residing in Lombardy appeared to be higher than in the general population of this region, these differences were not statistically significant (*P*-value = 0.11 and 0.10, respectively). Moreover, odds ratio (OR) for COVID-19 in CD was not statistically significant (OR 2.00, 95% CI 0.84–4.84; *P*-value = 0.12). Table 2 summarizes the results of the prevalence study.

Clinical features and outcomes of COVID-19 in coeliac patients

No significant differences for age at diagnosis of CD, age at recall, pattern of clinical presentation, gender duration and degree of adherence to a GFD and mucosal healing were found between coeliac patients who contracted COVID-19 and those who did not. Similarly, no differences were found in the demographic and clinical features

Table 3. Demographic and clinical features of coeliac patients who developed COVID-19

Patient (sex/age)	Type of CD [6]	GFD (months since diagnosis)	Comorbidities	Symptoms due to COVID-19 (duration)	Diagnostic method for COVID-19	Therapy for COVID-19	Admission to emergency room	Hospitalization	Mechanical ventilation	Outcome
Pt1 (F/40)	Non-classical	117	No	Dyspnoea, arthromyalgia, anosmia, ageusia, nausea, vomiting, diarrhoea (7 days)	Nasal swab	HCQ, LPV/r	Yes	No	No	Healed
Pt2 (F/24)	Classical	200	No	Fever, asthenia, arthromyalgia, anosmia, ageusia (10 days)	Nasal swab	No	No	No	No	Healed
Pt3 (M/27)	Classical	190	Bronchial asthma	Fever, sore throat (10 days)	Nasal swab	No	No	No	No	Healed
Pt4 (F/26)	Non-classical	83	Smoke	Fever, cold, anosmia ageusia (14 days)	Nasal swab, serology	No	No	No	No	Healed
Pt5 (F/47)	Non-classical	2	No	Fever, arthromyalgia (10 days)	Nasal swab, serology	No	No	No	No	Clinically healed, nasal swab still positive 80 days after symptoms
Pt6 (F/44)	Non-classical	38	No	Fever, cough, arthromyalgia, diarrhoea (14 days)	Serology	No	No	No	No	Healed
Pt7 (M/19)	Non-classical	4	Epilepsy	Fever, arthromyalgia, epileptic seizures (10 days)	Serology	No	No	No	No	Healed
Pt8 (F/53)	Classical	176	Breast cancer in remission	Cold, sore throat (5 days)	Serology	No	No	No	No	Healed
Pt9 (F/37)	Non-classical	93	No	Cold, cough, arthromyalgia, asthenia, ageusia, anosmia (10 days)	Serology	No	No	No	No	Healed

CD, coeliac disease; GFD, gluten-free diet; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; Pt, patients.

between patients with laboratory-confirmed COVID-19 and the group with COVID-like symptoms. These results are shown in Table 1.

None of the nine patients with COVID-19 required hospitalization and all were alive; Table 3 shows their clinical features. In the group of patients with COVID-like symptoms but no tests performed, one patient died. This patient was a 91-year-old man with a history of small-bowel adenocarcinoma complicating CD 12 years prior (2008). He resided in a nursing home where the epidemic began and died of acute respiratory distress syndrome in mid-March 2020. Although laboratory testing for COVID-19 was never performed, we feel that it is very likely that the death occurred because of COVID-19.

Discussion

This study describes the epidemiology of COVID-19 in adult patients affected by CD evaluated in a referral centre in Northern Italy. Incidence and prevalence of COVID-19 in coeliac patients are comparable with the general population in the Lombardy region, Northern Italy. No excess risk of COVID-19 was found in coeliac patients compared with the general population. This is in accordance with a recent report by a referral centre from North-East Italy, in which no cases of COVID-19 were ascertained in a group of 171 adult coeliac patients [29]. Similarly, our results are in line with another Italian paper that did not find an increased risk of SARS-CoV-2 infection in patients with chronic systemic autoimmune disorders compared to the general population [30] and with the fact that Italian coeliac patients do not perceive themselves to be at increased risk of COVID-19 [31].

Our results show that there is no substantial difference in terms of demographic and clinical features between coeliac patients who contracted COVID-19 and those who did not. Coeliac patients with COVID-19 were neither older than those who did not contract the infection, nor did they differ in terms of sex, pattern of clinical presentation according to the Oslo classification [6], duration and compliance to a GFD, and degree of mucosal healing. The fact that mucosal healing does not influence risk of COVID-19 is in line with previous studies suggesting that a certain risk of contracting infections persists despite good histological response to a GFD [15–17]. Indeed, we noticed that clinical features of coeliac patients who contracted COVID-19 are slightly different from the 'typical' profile of patients at risk of severe COVID-19 according to the literature and Italian health statistics [2,3]. Coeliac patients are younger and predominantly females, therefore this may be the reason why COVID-19 had a mild course in our affected patients.

This study has several limitations. First, we were not able to contact over the phone all the coeliac patients who have been followed-up since 2015. However, the proportion of patients we could not contact is less than 15%, and the only features that were different between these two groups were age at enrolment and duration of a GFD diet. We believe this is unlikely to significantly affect our overall results.

Second, in the 44 patients who had symptoms suggestive of COVID-19 but who were not tested, we could neither confirm nor exclude COVID-19. However, it is

widely recognized that this represents a common problem globally [32]. Moreover, our prevalence data do not take into consideration asymptomatic carriers of SARS-CoV-2, who, as suggested by a recent review, may be as high as 40–45% of all the cases [4].

We were not able to assess predictors of COVID-19 morbidity and mortality given our small sample size and the low event rate. In fact, none of the nine coeliac patients with laboratory-confirmed COVID-19 were hospitalized and none of them died. Only one patient died in the group with high suspicion of COVID-19. If we were to assume that this patient died because of COVID-19, then mortality in our cohort would be 1/324 (0.31%). A major limitation of this study is the possible difference in the age structure between coeliac patients and the general population. It is well known that the recent COVID-19 pandemic, particularly in Northern Italy, was more frequent and clinically more severe in subjects older than 70–80 years of age, an age group that is likely to be less represented in the CD group than in the general population. However, further comparisons are not possible in this regard. Finally, none of our patients affected by RCD contracted COVID-19. This is in line with a report by another major referral centre in the Lombardy Region, Northern Italy reporting no cases of COVID-19 among 21 patients affected by RCD [33]. Although RCD may theoretically be at risk of COVID-19 because of severe malnutrition and immunosuppressive therapies, it is likely that our small sample size did not allow further considerations. It is also possible that due to their frail health condition, they adopted adequate and stringent measures to protect themselves from infection.

In conclusion, our study shows that reassuringly coeliac patients are not at higher risk of contracting COVID-19 and their disease course is usually mild. For the time being, coeliac patients should adhere to the preventive measures suggested for the general population. Future studies on larger sample sizes are needed to confirm our data and to identify predictors of COVID-19 outcomes in coeliac patients.

Acknowledgements

A.S. and F.B. planned the study. A.S., S.M., M.L.N., E.A. and F.M.L. collected the data. E.A. performed the statistical analysis. A.S., E.A., F.B. and P.B. interpreted the data and drafted the manuscript. All the authors revised and approved the final version of the manuscript. Guarantor of the article: Prof. Federico Biagi, MD.

Conflicts of interest

There are no conflicts of interest.

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