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RESULTS FROM OBSERVATIONAL STUDIES IN REAL THERAPEUTIC PRACTICE IN PATIENTS WITH COVID-19

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Abstract. *The aim of the present work is to summarize the available data from observational studies performed in a real clinical setting of patients with active COVID-19 infection.A systematic review of publications in the scientific medical literature was conducted during the period from the beginning of the infection to the end of June, 2021. All of the 28 publications included in this review are full-text, observational studies published in English, conducted in a real clinical environment and present data on patients, who have been infected with COVID-19. Out of the 28 studies, 4 reviewed the possibility of a mother to infect her newborn during pregnancy or breastfeeding and found no risk to children. One study was related to children and adolescents of all races and included also patients with MIS-C and comorbidities. Non-invasive mechanical ventilation (HFNC) with a nasal cannula in patients with respiratory failure has been also explored and was reported to lead to a positive outcome. Three papers were dedicated to assessment of COVID-19 Standard of Care (SoC), in particular administration of hydroxychloroquine and doxycycline, favipiravir and remdesivir. Another three articles reviewed a large cohort of hospitalized patients with COVID-19. The mortality was higher in patients who were in the ICU. Observational studies of patients with COVID-19 in a real life setting are relatively limited, but provide valuable information on the risks of the disease in adults, children and newborns, as well as the treatment of complications of the infection.*

Key words: *COVID-19, real life clinical practice, observational studies, MIS-C, non-invasive mechanical ventilation*

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INTRODUCTION

The global spread of SARS-CoV-2 has been so extensive that the WHO declared COVID-19 a pandemic on March 11, 2020 [1]. The COVID-19 pandemic has shaken humanity over the past two years and changed lifestyles and medical practices [2]. Numerous studies on the development of the infection, its possible complications and the variability of the SARS-COV-2 virus have enriched medical science [3]. The majority of studies have focused on the virus and the possibility of disease prevention, both as a sanitary measure and as an active immunization and it's impact [4-6]. However, studies in a real therapeutic environment are relatively limited, which has led to our interest in this research. The aim of the present work is to summarize the available data from observational studies performed in a real clinical setting of patients with active COVID-19 infection.

METHODOLOGY

A systematic review of publications in the scientific medical literature was conducted during the period from the beginning of the infection to the end of June, 2021. The publications were identified from the PubMed database with search keywords “COVID 19 AND observational AND real-life”. PubMed’s database was selected as the leading, specialized scientific database for medical literature, which covers the largest number of indexed journals.

During the search, a total of 49 publications were identified. 19 were excluded after analyzing the abstracts and the full texts of 30 publications were left (Figл 1). The reasons for exclusion were as follows: 7 publications addressed lifestyle issues during a pandemic, 4 addressed the impact of sanitary protection measures, 8 addressed populations for which there was no evidence of COVID-19 infection. An additional two studies were excluded after evaluation of the full text, as they were either ongoing and didn’t report final results, or were only a protocol for a future study. All of the 28 publications included in this review are full-text, observational studies published in English, conducted in a real clinical environment and present data on patients, who have been infected with COVID-19.

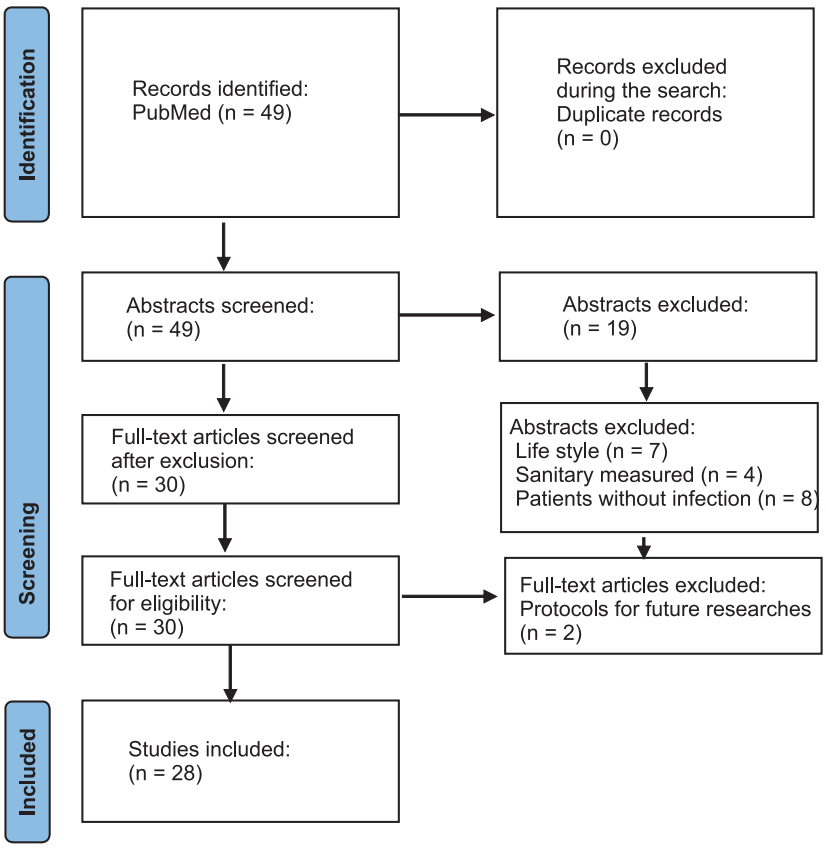

Fig. 1. PRISMA flow diagram for selection of studies [7]

RESULTS

The publications were systematized by author, number of patients, included in the study, methodology, results and conclusion of the authors (Table 1). Out of the 28 studies, 4 reviewed the possibility of a mother to infect her newborn during pregnancy or breastfeeding and found no risk to children. One study was related to children and adolescents of all races and included also patients with multisystem inflammatory syndrome in children (MIS-C) and comorbidities. The research concluded that children, who met MIS-C criteria were more likely to be admitted to critical care, however the children and young people had less severe acute symptoms than adults. One publication evaluated the treatment of patients with respiratory failure with non-invasive mechanical ventilation with a nasal cannula (HFNC) after failure of CPAP or NIV and reported positive outcome, but in fact the method was time and resources consuming. Three papers were dedicated to assessment of COVID-19 Standard of Care (SoC), in particular administration of hydroxychloroquine and doxycycline, favipiravir and remdesivir. The most patients were managed adequately by SoC and discharged with negative PCR test. Another three articles reviewed a large cohort of hospitalized patients with COVID-19. The studies found higher mortality especially in men with chronic diseases and with increasing age. Similar study was conducted among patients in hospital, but including comparison between outcome of patients who needed and who didn’t need intensive care unit (ICU). The mortality was higher in patients who were in the ICU. Hospitalized patients with COVID-19 and HIV infections were assessed and no higher mortality was found. Several studies reviewed the treatment with NSAIDS, statins, ACEIs/ARBs and their positive impact to prevent complications of the COVID-19 infection. Publication related to evaluation of kinetics of the neutralizing antibody response showed that antibody protection declined during the reviewed period of 94 days. Another publication assessed HRQoL in patients with COVID-19 pneumonia and concluded significant improvement of HRQoL 15 days after discharge. Quality of life (QoL) and frequency of exacerbations in patients with asthma were also investigated and no additional risk of developing the infection was reported.

Table1. Systematic review of included studies

Authors	Nr and patient characteristics	Methodology of research and treatment	Main results	Author's conclusions
Procopio G., et al. 8	Five patients with a high-throughput nasal cannula for oxygen therapy.	Oxygen therapy	The experience with five patients treated with Non-Invasive Mechanical Ventilation (HFNC) with a nasal cannula after after failure of CPAP or NIV was positive. All five patients were discharged healthy, but the therapy was time consuming and involves a lot of resources.	Non-invasive mechanical ventilation (HFNC) can be used successfully in selected patients with COVID-19.
Faizul H. A. et al. 9	32 patients with similar therapy.	Standard of care (SoC), administration of hydroxychloroquine and doxycycline, 9 patients were on favipiravir. Patients were followed after discharge and PCR tests were performed 2 days after discharge.	No deaths were reported. The average hospital stay was 13.9 days and varies between 8-21 days. All were discharged with improved subjective symptoms and a negative SARS-CoV-2 test. Vital signs (heart rate and blood pressure), electrolyte levels and blood counts were within normal, acceptable limits.	The study raises optimism about the application of standard of care and the applied treatment protocols for COVID-19.
Docherty A. B. et al.10	20 133 hospitalized Covid-19 patients	Study of the characteristics and risk factors of patients included in the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC).	The median age of patients admitted to hospital with covid-19, or with a diagnosis of covid-19 made in hospital, was 73 years . More men were admitted than women (men 60%, n=12 068; women 40%, n=8065). The median duration of symptoms before admission was 4 days. The commonest comorbidities were chronic cardiac disease, uncomplicated diabetes , non-asthmatic chronic pulmonary disease, and chronic kidney disease; 23% had no reported major comorbidity. Overall, 41% of patients were discharged alive, 26% died, and 34% continued to receive care at the reporting date. 17% required admission to high dependency or intensive care units; of these, 28% (were discharged alive, 32% died, and 41% continued to receive care at the reporting date. Of those receiving mechanical ventilation, 17% were discharged alive, 37% died, and 46% remained in hospital. Increasing age, male sex, and comorbidities including chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity were associated with higher mortality in hospital.	ISARIC WHO CCP-UK is a large prospective cohort study of patients in hospital with covid-19. The study continues to enrol at the time of this report. In study participants, mortality was high, independent risk factors were increasing age, male sex, and chronic comorbidity, including obesity. This study has shown the importance of pandemic preparedness and the need to maintain readiness to launch research studies in response to outbreaks.
Salvatore C. M. et al. 11	1481 newborns	The women in labor were positive for SARS-CoV-2. Newborns were tested for SARS-CoV-2 at 24 hours, days 5-7, and 14 days and were followed up by telemedicine for up to 1 month.	Of 1481 deliveries, 116 (8%) mothers tested positive for SARS-CoV-2; 120 neonates were identified. All neonates were tested at 24 h of life and none were positive for SARS-CoV-2. 82 (68%) neonates completed follow-up at day 5-7 of life. Of the 82 neonates, 68 (83%) roomed in with the mothers. All mothers were allowed to breastfeed; at 5-7 days of life, 64 (78%) were still breastfeeding. 79 (96%) of 82 neonates had a repeat PCR at 5-7 days of life, which was negative in all; 72 (88%) neonates were also tested at 14 days of life and none were positive.	These results suggest that perinatal transmission of COVID-19 is unlikely to occur if correct hygiene precautions are undertaken, and that allowing neonates to room in with their mothers and direct breastfeeding are safe procedures when paired with effective parental education of infant protective strategies.

Continuation of table 1

Swann O. V. 12	651 children and adolescents up to 19 years of age admitted to hospital with SARS-CoV-2.	Median age was 4.6 years, 35% were under 12 months old, and 56% were male. 57% (were white, 12% South Asian, and 10% black. 42% had at least one recorded comorbidity. A systemic mucocutaneous-enteric cluster of symptoms was identified, which encompassed the symptoms for the WHO MIS-C criteria. 18% (116/632) of children were admitted to critical care. On multivariable analysis, this was associated with age under 1 month, age 10-14 years and black ethnicity. Six (1%) of 627 patients died in hospital, all of whom had profound comorbidity. 11% (52/456) met the WHO MIS-C criteria, with the first patient developing symptoms in mid-March.	Children meeting MIS-C criteria were older (median age 10.7) and more likely to be of non-white ethnicity (64% (29/45) v 42% (148/355); P=0.004). Children with MIS-C were five times more likely to be admitted to critical care (73% (38/52) v 15% (62/404); P<0.001). In addition to the WHO criteria, children with MIS-C were more likely to present with fatigue (51%), headache (34%); myalgia (34%), sore throat (30%), and lymphadenopathy (20%). No deaths occurred in the MIS-C group.	Conclusions: Children and young people have less severe acute covid-19 than adults. A systemic mucocutaneous-enteric symptom cluster was also identified in acute cases that shares features with MIS-C. This study provides additional evidence for refining the WHO MIS-C preliminary case definition. Children meeting the MIS-C criteria have different demographic and clinical features depending on whether they have acute SARS-CoV-2 infection (polymerase chain reaction positive) or are post-acute (antibody positive).
Seow J. et al. 13	65 patients during COVID-19 infection	Using sequential serum samples collected up to 94 days post onset of symptoms (POS) from 65 individuals with real-time quantitative PCR-confirmed SARS-CoV-2 infection, we show seroconversion (immunoglobulin (Ig)M, IgA, IgG) in >95% of cases and neutralizing antibody responses when sampled beyond 8 d POS.	This study showed that the kinetics of the neutralizing antibody response is typical of an acute viral infection, with declining neutralizing antibody titres observed after an initial peak, and that the magnitude of this peak is dependent on disease severity. Although some individuals with high peak infective dose (ID50 > 10,000) maintained neutralizing antibody titres >1,000 at > 60 d POS, some with lower peak ID50 had neutralizing antibody titres approaching baseline within the follow-up period. A similar decline in neutralizing antibody titres was observed in a cohort of 31 seropositive healthcare workers.	The present study has important implications when considering widespread serological testing and antibody protection against reinfection with SARS-CoV-2, and may suggest that vaccine boosters are required to provide long-lasting protection.
Santus P. 14	20 patients with pneumonia caused by COVID-19	In a real-life observational study, 20 patients with COVID-19-related pneumonia received usual care plus erdosteine (300 mg twice daily) for 15 days after hospital discharge following local standard operating procedures. At discharge (T0) and on Day 15 (T1), participants completed the St George's Respiratory Questionnaire (SGRQ), the modified Medical Research Council (mMRC) scale of dyspnoea during daily activity, the BORG scale for dyspnoea during exertion, and Visual Analogue Scale (VAS) for dyspnoea at rest. Paired t-tests compared scores at T0 and T1.	The mean (SD) SGRQ total score decreased from 25.5 (15.5) at T0 to 16.9 (13.2) at T1 (p<0.01); 65% of patients achieved a clinically important change of ≥4 points. SGRQ domain scores (symptoms, activity, and impact) were also significantly reduced (all p<0.01). The mean (SD) VAS score decreased from 1.6 (1.7) to 1.4 (2.5); p<0.01. The mean mMRC score decreased significantly (p=0.031) and 30% of patients achieved a clinically important change of ≥1 point. The mean (SD) Borg score increased from 12.8 (4.2) to 14.3 (2.4); p<0.01.	The present proof of concept study is the first to report HRQoL in patients with COVID-19. During 15 days after hospital discharge, patients reported significant improvements in HRQoL and dyspnoea at rest and during daily activities.
Gervasoni C. et al.. 15	47 patients with HIV and COVID-19 infection	Hospitalized patients with both infections	Patients treated for HIV and admitted to hospital with SARS-CoV-2 were followed up. Out of the 47 people, 45 (96%) fully recovered, 2 died from complications of both infections.	There were two deaths and the others recovered, indicating that mortality is close to the normal population.

Continuation of table 1

Liu R et.al. 16	31 patients with confirmed COVID-19 infection with and without comorbidities.	Coronavirus disease 2019 (COVID-19) has caused a global pandemic associated with substantial morbidity and mortality. Naso-pharyngeal swabs and sputum samples are generally collected for serial viral load screening of respiratory contagions, but temporal profiles of these samples are not completely clear in patients with COVID-19.	Samples from each patient were obtained, and serial viral load was measured by real-time quantitative polymerase chain reaction. The authors found that the viral load in the sputum was inclined to be higher than samples obtained from the nasopharyngeal swab at disease presentation. Moreover, the viral load in the sputum decreased more slowly over time than in the nasopharyngeal group as the disease progressed. Interestingly, even when samples in the nasopharyngeal swab turned negative, it was com-monly observed that patients with underlying diseases, especially hypertension and diabetes, remained positive for COVID-19 and required a longer period for the sputum samples to turn negative.	These combined findings emphasize the importance of tracking sputum samples even in patients with negative tests from nasopharyn-geal swabs, especially for those with underlying conditions.In conclusion, this work reinforces the importance of sputum samples for SARS-CoV-2 detection to minimize transmission of COVID-19 within the community.
Molteni E. et al. 17	To test the hypothesis that pregnant women in commu-nity differ in their COVID-19 symptoms profile and disease severity compared to non-pregnant women.	400,750 UK, Sweden and US women (79 pregnant who tested positive) who self-reported symptoms and events longitudinally via their smartphone, and a replication cohort drawn from 1,344,966 USA women (162 pregnant who tested positive) cross-sectional self-reports samples from the social media active user base. The study compared frequencies of symptoms and events, including self-reported SARS-CoV-2 testing and differences between pregnant and non-pregnant women who were hospitalized and those who recovered in the community. Multivariable regression was used to investigate disease severity and comorbidity effects.	Pregnant and non-pregnant women positive for SARS-CoV-2 infection drawn from these community cohorts were not different with respect to COVID-19-related severity. Pregnant women were more likely to have received SARS-CoV-2 testing than non-pregnant, despite reporting fewer clinical symptoms. Pre-existing lung disease was most closely associated with the severity of symptoms in preg-nant hospitalized women. Heart and kidney diseases and diabetes were additional factors of increased risk. The most frequent symptoms among all non-hospitalized women were anosmia [63% in pregnant, 92% in non-pregnant] and headache [72%, 62%]. Cardiopulmonary symptoms, includ-ing persistent cough [80%] and chest pain [73%], were more frequent among pregnant women who were hospital-ized. Gastrointestinal symptoms, including nausea and vomiting, were different among pregnant and non-pregnant women who developed severe outcomes.	Although pregnancy is widely considered a risk factor for SARS-CoV-2 infection and outcomes, and was associated with higher propensity for testing, the profile of symptom characteristics and severity in our community-based cohorts were comparable to those observed among non-pregnant women, except for the gastrointes-tinal symptoms. Consistent with observations in non-pregnant populations, comorbidities such as lung disease and diabetes were associated with an increased risk of more severe SARS-CoV-2 infection during pregnancy. Pregnant women with pre-existing conditions require careful monitoring for the evolution of their symptoms during SARS-CoV-2 infection.
Bertino E. et al.. 18	14 breastfeeding women	The aim of the study was to look for the pres-ence of SARS-CoV-2 RNA in the milk of a group of SARS-CoV-2 positive mothers. This was a prospective collaborative observational study where samples of human milk from 14 breastfeeding mothers positive for SARS-CoV-2 were collected. A search of viral RNA in breast milk samples was performed by RT-PCR methodology tested for human milk. All the newborns underwent a clinical follow up during the first month of life or until the finding of two sequential negative swabs.	In 13 cases the search for SARS-CoV-2 RNA in milk samples resulted negative and in one case it was positive. Thirteen of the 14 newborns were exclusively breastfed and closely monitored in the first month of life. Clinical outcome was uneventful. Four newborns tested positive for SARS-CoV-2 and were all detected in the first 48 h of life, after the onset of maternal symptoms. Also the clinical course of these 4 infants, including the one who received mother's milk positive for SARS-CoV-2, was uneventful, and all of them became SARS-CoV-2 negative within 6 weeks of life. Conclusion:	The study supports the results that mothers infected with SARS-CoV-2 are not at risk of infect-ing their newborns during breastfeeding.

Continuation of table 1

Snipelisky D et al. 19	156 hospitalized patients in the intensive care unit.	The observational study included consecutive patients admitted to a large community teaching hospital with a diagnosis of SARS-CoV-2 between March 6, 2020 and March 31, 2020. Comparisons were made based on the need for ICU admission.	A total of 156 patients were admitted, 42 of whom (26.9%) required ICU admission and 114 (73.1%) did not. No difference in age (61.9 years vs 60.5 years, P = 0.67), race/ethnicity, or comorbidities were noted, except that patients requiring ICU care had lower serum albumin levels and lymphocyte counts and higher liver function tests, white blood cell count, and absolute neutrophil count on admission. The average time from admission to death was similar (10 days in an ICU subset vs 9.2 days in a non-ICU subset, P = 0.78), yet patients necessitating ICU care had longer hospital lengths of stay (10.2 vs 5.1 days, P = 0.0002). At the time of data extraction, 15 patients in the ICU had died, 7 were discharged from the hospital, and 20 were still admitted while 5 patients died in the non-ICU cohort with 97 discharged and 12 patients admitted.	This is the largest study assessing clinical differences based on the need for ICU admission in inpatients with SARS-CoV-2. It found few major differences in clinical variables between subsets. Among patients admitted to the ICU, outcomes were generally poor.
Bhuyan M. Ar. et al. 20	33 patients	All patients in this cohort were positive for SARS-CoV-2 by PCR and they attended the hospital with variable presenting symptoms those ranged from cough and fever to respiratory distress and pneumonia. As per the protocol, the patients were regularly evaluated for several parameters of COVID-19-related pathology. Before discharge, they were checked for SARS-CoV-2 for 2 consecutive times. The management strategy included standard of care (SoC) and administration of hydroxychloroquine and azythromycin, available in Bangladesh.	Out of total 33 patients, 1 patient died at day 4 day after admission. Two patients developed severe complications and were referred to tertiary hospital in Dhaka (2 and 3 days after admission), the capital of Bangladesh, where they recovered and were discharged from hospital after being SARS-CoV-2 negative. The rest 30 patients were discharged from the medical college hospital after being negative for SARS-CoV-2 in two subsequent assessments and improvement of their COVID-related symptoms. The average hospital stay of these patients was 14.5 days with a range of 10-24 days.	It seems that most of the COVID-19 patients may be adequately managed by standard of care management with drug support. However, early diagnosis and hospitalization with adequate care may be important variables for better survival. These factors may be properly ensured if the patient burden remains at a palatable level in forthcoming days in Bangladesh.
Munblit D. et al.. 21	4261 hospitalized patients	We extracted data from the medical records of adult patients who were consecutively admitted for suspected COVID-19 infection in Moscow between 8 April and 28 May 2020.	Out of the 4261 patients hospitalized for suspected COVID-19, outcomes were available for 3480 patients (median age, 56 years; interquartile range, 45-66). The most common comorbidities were hypertension, obesity, chronic cardiovascular disease, and diabetes. Half of the patients (n = 1728) had a positive reverse transcriptase-polymerase chain reaction (RT-PCR), while 1748 had a negative RT-PCR but had clinical symptoms and characteristic computed tomography signs suggestive of COVID-19. No significant differences in frequency of symptoms, laboratory test results, and risk factors for in-hospital mortality were found between those exclusively clinically diagnosed or with positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RT-PCR. In a multivariable logistic regression model the following were associated with in-hospital mortality: older age (per 1-year increase; odds ratio, 1.05; 95% confidence interval, 1.03-1.06), male sex (1.71; 1.24-2.37), chronic kidney disease (2.99; 1.89-4.64), diabetes (2.1; 1.46-2.99), chronic cardiovascular disease (1.78; 1.24-2.57), and dementia (2.73; 1.34-5.47).	Age, male sex, and chronic comorbidities were risk factors for in-hospital mortality. The combination of clinical features was sufficient to diagnose COVID-19 infection, indicating that laboratory testing is not critical in real-life clinical practice.

Continuation of table 1

Hughes H. E., et al. 22		The Public Health England Emergency Department Syndromic Surveillance System (EDSSS) carries out daily (near real-time) public health surveillance of emergency department (ED) attendances across England. This retrospective observational analysis of EDSSS data aimed to describe changes in ED attendances during March-April 2020, and identify the attendance types with the largest impact.	Type 1 ED attendances were selected from 109 EDs that reported data to EDSSS for the period 1 January 2019 to 26 April 2020. The daily numbers of attendances were plotted by age group and acuity of presentation. The 2020 'COVID-19' period (12 March 2020 to 26 April 2020) attendances were compared with the equivalent 2019 'pre-COVID-19' period (14 March 2019 to 28 April 2019): in total; by hour and day of the week; age group(<1, 1-4, 15-14, 15-44, 45-64 and 65+ years); gender; acuity; and for selected syndromic indicators(acute respiratory infection, gastroenteritis, myocardial ischaemia). Daily ED attendances up to 11 March 2020 showed regular trends, highest on a Monday and reduced in children during school holidays. From 12 March 2020 ED attendances decreased across all age groups, all acuity levels, on all days and times. Across age groups the greatest percentage reductions were seen in school age children (5-14 years). By acuity, the greatest reduction occurred in the less severe presentations. Syndromic indicators showed that the greatest reductions were in non-respiratory indicators, which fell by 44-67% during 2020 COVID-19, while acute respiratory infection was reduced by -4.4% (95% CI -9.5% to 0.6%).	ED attendances in England have been particularly affected during the COVID-19 pandemic due to changes in healthcare seeking behaviour. EDSSS has enabled real-time daily monitoring of these changes, which are made publicly available to facilitate action. The EDSSS provides valuable surveillance of ED attendances in England. The flexibility of EDSSS allowed rapid development of new indicators (including COVID-19-like) and reporting methods.
Garcia-Vidal C., et al. 23	123 patients hospitalized with COVID-19	We performed a descriptive study of all patients admitted for ≥48 hours with confirmed COVID-19 who received remdesivir between the 1st of July and the 30th of September 2020.	A total of 123 patients out of 242 admitted with COVID-19 at our hospital (50.8%) received remdesivir. Median age was 58 years, 61% were males and 56.9 % received at least one anti-inflammatory treatment. No adverse events requiring remdesivir discontinuation were reported. The need of intensive care unit admission, mechanical ventilation and 30-days mortality were 19.5%, 7.3% and 4.1%, respectively.	In our real-life experience, the use of remdesivir in hospitalized patients with COVID-19 was associated with a low mortality rate and good safety profile.
McPadden J., et al. 24	7995 patients with proven infection from a database of 28605 people	This was an observational, retrospective study based on real-world data for 7,995 patients with SARS-CoV-2 from a clinical data repository. Main outcome and performance measures: Primary outcomes were admission and in-hospital mortality for patients with SARS-CoV-2 infection as determined by RT-PCR testing. We also assessed features associated with the need for respiratory support.	Of the 28605 patients tested for SARS-CoV-2, 7995 patients (27.9%) had an infection (median age 52.3 years) and 2154 (26.9%) of these had an associated admission (median age 66.2 years). Of admitted patients, 2152 (99.9%) had a discharge disposition at the end of the study period. Of these, 329 (15.3%) required invasive mechanical ventilation and 305 (14.2%) expired. Increased age and male sex were positively associated with admission and in-hospital mortality (median age 80.7 years), while comorbidities had a much weaker association with the risk of admission or mortality. Black race (OR 1.43, 95%CI 1.14-1.78) and Hispanic ethnicity (OR 1.81, 95%CI 1.50-2.18) were identified as risk factors for admission, but, among discharged patients, age-adjusted in-hospital mortality was not significantly different among racial and ethnic groups.	This observational study identified, among people testing positive for SARS-CoV-2 infection, older age and male sex as the most strongly associated risks for admission and in-hospital mortality in patients with SARS-CoV-2 infection. While minority racial and ethnic groups had increased burden of disease and risk of admission, age-adjusted in-hospital mortality for discharged patients was not significantly different among racial and ethnic groups. Ongoing studies will be needed to continue to evaluate these risks, particularly in the setting of evolving treatment guidelines.

Continuation of table 1

Efficace F., et al. 25	116 patients	The main objectives of this web-based platform are to generate relevant data to better understand quality of life, symptoms, and medication adherence during the COVID-19 pandemic and postpandemic era; to develop a prospective real-life registry on outcomes of patients with hematologic cancer, with or without a diagnosis of COVID-19; and to facilitate patient-centered care in routine practice.	Results: Recruitment of participants started in December 2020. As of April 2021, a total of 116 patients have been enrolled in this study. Use of this platform may help to improve patient-physician communication and help hematologists in the early recognition of clinically important problems and symptoms of their patients. More than 20 community and university-based hospitals have currently agreed to participate. In addition to patient-reported outcome data, the prospective collection of disease- and treatment-related information, as well as data on possible COVID-19 diagnosis and COVID-19 vaccination, will allow the development of a large database to also identify subgroups of patients at risk of poor outcomes.	Data generated via this platform will help to answer clinically relevant questions for patients with hematologic malignancies during the COVID-19 pandemic and postpandemic era. The use of the GIMEMA-ALLIANCE platform in routine practice may also contribute to enhancing patient-centered care.
Denis F., et al. 26	548 patients with olfactory dysfunction	We aimed to quantify the benefit of olfactory training and visual stimulation assisted by a dedicated web application for patients who experienced olfactory dysfunction for ≥1 month. Methods: We performed an observational, real-life, data-based study on a cohort of patients who experienced at least 1 month of persistent olfactory dysfunction.	In total, 548 patients were assessable for primary outcome assessment. The mean baseline, self-assessed olfactory score was 1.9 (SD 1.7), and this increased to 4.6 (SD 2.8) after a mean olfactory training time of 27.7 days (SD 17.2). Olfactory training was associated with at least a 2-point increase in 64.2% (352/548) of patients. The rate of patients' olfactory improvement was higher for patients who trained for more than 28 days than that rate for patients who trained for less than 28 days (73.3% vs 59%; P=.002). The time to olfactory improvement was 8 days faster for patients with hyposmia compared to the time to improvement for patients with anosmia (P<.001). This benefit was observed regardless of the duration of the olfactory dysfunction.	Olfactory training and visual stimulation assisted by a dedicated web application was associated with significant improvement in olfaction, especially after 28 days of olfactory training.
Caruso C., et al. 27	100 patients with severe COVID-19 infection	A survey was conducted to evaluate the effects on adherence, exacerbations and quality of life in patients with severe asthma during the COVID-19 pandemic period. Methods: 100 severe asthma patients, who accepted to participate to the survey, were asked to respond to different questionnaires in order to assess asthma symptoms (Asthma Control Test - ACT, and Asthma Control Quality - ACQ) and rino-sinusal ones (Sino-nasal outcome test - SNOT-22).	Results: 31 out of 100 patients reported worsening of respiratory symptoms requiring a step-up in therapy dosage or frequency during the observational period; however, exacerbation rate was very low. Only 17 (17%) of the 100 participants experienced a severe asthma exacerbation. Moreover, there was no confirmed diagnosis of COVID-19 in this population.	Conclusion: Patients with severe asthma did not show higher rates of exacerbations during the pandemic outbreak as well as no increased risk of contracting COVID-19 infection or developing the disease. Self-administration of biological drugs could be useful to maintain high rates of adherence to therapy, and, at the same time, to decrease the risk of exacerbations or Intensive Care Unit (ICU) room access.
Kelleni M. T. 28	Not mentioned	We analyze selected studies that correlated COVID-19 with dysregulated interferon and inflammatory responses while reflecting on our academic and real-life experience using non-steroidal anti-inflammatory drugs, nitazoxanide and azithromycin for management of COVID-19.	Moreover, we interpret the results that suggested a potential survival benefit of low-dose aspirin and colchicine when used for COVID-19. Nitazoxanide/azithromycin combination has been first hypothesized by the author and practiced by him and several researchers to benefit COVID-19 patients due to a potential ability to augment the natural interferon response as well as their positive immunomodulatory effects on several cytokines.	Furthermore, NSAIDs, that are unfortunately currently at best of second choice after paracetamol, have been early postulated and clinically practiced by the author to prevent or ameliorate COVID-19 complications and mortality due to their anti-inflammatory and immunomodulatory properties. Finally, we repeat our previous call to adopt our observational study that used these drugs in sufficiently powered double blind randomized clinical trials.

Continuation of table 1

Nayak M. K., et al. 29	165 patients	This prospective observational study was conducted in Kalinga Institute of Medical Science (KIMS), Odisha state from 1st May to 20th October 2020. A total of 165 neonates born to SARS-CoV-2 infected mothers were enrolled. Real time polymerase chain reaction (RT PCR) testing was done in first 32 neonates in initial 24 h of life.	The clinical characteristics of 162 mothers & 165 neonates were analyzed. Mode of delivery was by caesarian section in most (n = 103, 60%) cases. Three (3/32, 9.4%) inborn and 6 outborn neonates were SARS-CoV-2 positive. Thirty-eight (23%) babies needed neonatal intensive care. Clinical characteristics of neonates were meconium-stained amniotic fluid (MSAF [23.63%]), prematurity (16.9%), respiratory distress (10.5%), moderate to severe hypoxic ischemic encephalopathy (3.6%), sepsis (7%) and hyperbilirubinemia (8.7%). Out of 138 stable babies kept on mother side and initiated breast feeding, none of them developed any signs and symptoms attributable to SARS-CoV-2. Five (3%) neonates died in COVID hospital of which one baby was SARS-CoV-2 positive.	There was an increased rate of incidences of hypoxic ischemic encephalopathy, meconium stained liquor and cesarean section delivery in COVID hospital. We found a possible vertical transmission in 9.4% cases. None of the neonates developed sign and symptoms of SARS-CoV-2 infection during rooming in and breast feeding.
Di Castelnuovo A., et al. 30	3451 patients	To describe the association between lopinavir/ritonavir (LPV/r) or darunavir/cobicistat (DRV/c) use and in-hospital mortality in COVID-19 patients. Study Design: Multicenter observational study of COVID-19 patients admitted in 33 Italian hospitals. Medications, preexisting conditions, clinical measures, and outcomes were extracted from medical records. Patients were retrospectively divided in three groups, according to use of LPV/r, DRV/c or none of them. Primary outcome in a time-to event analysis was death. We used Cox proportional-hazards models with inverse probability of treatment weighting by multinomial propensity scores.	Out of 3,451 patients, 33.3% LPV/r and 13.9% received DRV/c. Patients receiving LPV/r or DRV/c were more likely younger, men, had higher C-reactive protein levels while less likely had hypertension, cardiovascular, pulmonary or kidney disease. After adjustment for propensity scores, LPV/r use was not associated with mortality (HR = 0.94, 95% CI 0.78 to 1.13), whereas treatment with DRV/c was associated with a higher death risk (HR = 1.89, 1.53 to 2.34, E-value = 2.43). This increased risk was more marked in women, in elderly, in patients with higher severity of COVID-19 and in patients receiving other COVID-19 drugs.	Conclusions: In a large cohort of Italian patients hospitalized for COVID-19 in a real-life setting, the use of LPV/r treatment did not change death rate, while DRV/c was associated with increased mortality. Within the limits of an observational study, these data do not support the use of LPV/r or DRV/c in COVID-19 patients.
Prasad A., et al. 31	50 patients	To detect SARS-CoV-2 in expressed breast milk (EBM) of mothers infected with SARS-CoV-2 and clinical outcome of neonates delivered and breast fed by them. Design: A single-centre, prospective observational study involving 50 SARS-CoV-2-infected mothers and their 51 neonates. Setting: A tertiary care hospital in Eastern India. Participants: SARS-CoV-2-infected mothers and neonates delivered by them. Main outcome measures: We investigated the presence of SARS-CoV-2 in the breast milk of mothers, who tested positive for this virus in their nasopharyngeal swab (NPS).	50 SARS-CoV-2-positive expectant mothers were enrolled for the study. One out of 51 neonates, who delivered through lower segment caesarean section at term gestation and tested SARS-CoV-2 negative, died due to severe birth asphyxia. One sample of EBM was collected from each of the 49 mothers within 4 days of delivery. All EBM samples tested negative for SARS-CoV-2 through real-time reverse transcriptase-PCR (RT-PCR). All the newborns were screened twice for presence of SARS-CoV-2 RNA in their NPS, by RT-PCR. 2 of 51 neonates had COVID-19 infection after 24 hours of life. Caregivers of 37 of 50 alive neonates responded to follow-up via telephone. Except for minor feed intolerance in one (1 of 37) neonate, all neonates were reported well after 1 month of their age.	Conclusion: All the samples of breast milk were negative for SARS-CoV-2. Most of the neonates remained asymptomatic on breast feeding, whose mothers had SARS-CoV-2 infection before delivery.

Continuation of table 1

van Hensbergen M., и et al. 32		In this study we aimed to determine whether cross-border introduction of the virus took place by analysing the LTCF outbreak in Sittard, both epidemiologically and microbiologically.	Methods: Surveys and semi-structured oral interviews were conducted with all present LTCF residents by health care workers during regular points of care for information on new or unusual signs and symptoms of disease. Both throat and nasopharyngeal swabs were taken from residents suspect of COVID-19, based on regional criteria, for the detection of SARS-CoV-2 by Real-time Polymerase Chain Reaction. Additionally, whole genome sequencing was performed using a SARS-CoV-2 specific amplicon-based Nanopore sequencing approach. Moreover, twelve random residents were sampled for possible asymptomatic infections. Results: Out of 99 residents, 46 got tested for COVID-19. Out of the 46 tested residents, nineteen (41%) tested positive for COVID-19, including 3 asymptomatic residents. CT-values for asymptomatic residents seemed higher compared to symptomatic residents. Eleven samples were sequenced, along with three random samples from COVID-19 patients hospitalized in the regional hospital at the time of the LTCF outbreak. All samples were linked to COVID-19 cases from the cross-border region of Heinsberg, Germany.	Conclusions: Sequencing combined with epidemiological data was able to virtually prove cross-border transmission at the start of the Dutch COVID-19 epidemic. Our results highlight the need for cross-border collaboration and adjustment of national policy to emerging region-specific needs along borders in order to establish coordinated implementation of infection control measures to limit the spread of COVID-19.
Byttebier G., et al. 33	959 patients	For this reason, we undertook an observational study in four Belgian hospitals to determine whether in-hospital treatment with these drugs could improve survival in 959 COVID-19 patients.	We found that treatment with statins and ACEIs/ARBs reduced 28-day mortality in hospitalized COVID-19 patients. Moreover, combination treatment with these drugs resulted in a 3-fold reduction in the odds of hospital mortality (OR = 0.33; 95% CI 0.17-0.69).	These findings were in general agreement with other published studies. Additional observational studies and clinical trials are needed to convincingly show that in-hospital treatment with statins, ACEIs/ARBs, and especially their combination saves lives.
Lebourgeois S., et al. 34	277 patients	Objective: The aim of this study was to evaluate the QIAstat-Dx® Respiratory SARS-CoV-2 Panel (QIAstat-SARS-CoV-2), which is a closed, fully automated, multiplex polymerase chain reaction (PCR) assay that detects severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 21 other pathogens that cause respiratory disease	Results: In total, 189 negative and 88 positive samples were analyzed. QIAstat-SARS-CoV-2 had an NPA of 90.48% and a PPA of 94.32% . Co-infections were detected by QIAstat-SARS-CoV-2 in 4/277 specimens. The methods exhibited comparable failure rates (23/307 [7.5%] vs. 6/298 [2.0%] for QIAstat-SARS-CoV-2 and reference methods, respectively). The turnaround time was shorter for QIAstat-SARS-CoV-2 compared with the reference method (difference in mean -14:30 h [standard error, 0:03:23; 95% CI, -14:37, -14:24]; P < 0.001).	Conclusions: QIAstat-SARS-CoV-2 shows good agreement with the reference assay, providing faster and accurate results for detecting SARS-CoV-2.

DISCUSSION

As far as we know, this is the first systematic review of published, observational studies conducted in real conditions with patients with proven COVID-19 infection. Our systematic review identified a limited number of observational studies, despite our expectations. This could be explained by the risk to physicians and researchers conducting real-world studies in patients who are highly virulent. Another possible reason is that the attention of most researchers has been focused on the development of vaccines, as well as vaccination coverage. There are also limited studies on the long-term effects of COVID-19 and their treatment. Long-term effects of COVID-19, such as olfactory dysfunction, time to full recovery, etc., need to be further investigated.

One limitation of the current review is that the literature search was limited to only one database (PubMed) and articles appearing in journals, not included in PubMed, or in languages other than English were not identified.

CONCLUSION

Observational studies of patients with COVID-19 in a real life are relatively limited, but provide valuable information on the risks of the disease in adults, children and newborns, as well as the treatment of complications of the infection.

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