I BEST OF THE WEEK (21 feb – 27 feb 2022)

Articolo	Abstract	Contenuto e Commento
Parmar H. et al. BMC Infect Dis. RT-PCR negative COVID-19. https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/s12879-022-07095-x.pdf	Abstract Background: COVID-19 is a multi-system infection with emerging evidence-based antiviral and anti-inflammatory therapies to improve disease prognosis. However, a subset of patients with COVID-19 signs and symptoms have repeatedly negative RT-PCR tests, leading to treatment hesitancy. We used comparative serology early in the COVID-19 pandemic when background seroprevalence was low to estimate the likelihood of COVID-19 infection among RT-PCR negative patients with clinical signs and/or symptoms compatible with COVID-19. Methods: Between April and October 2020, weconductedserologictesting of patients with (i) signs and symptoms of COVID-19 whowererepeatedlynegative by RT-PCR ('Probables'; N = 20), (ii) signs and symptoms of COVID-19 but with a potential alternative diagnosis ('Suspects'; N = 15), (iii) no signs and symptoms of COVID-19 ('Non-suspects';	Studio condotto tra aprile e ottobre 2020, quando ancora la sieroprevalenza per SARS-CoV-2 era ancora globalmente modesta, per valutare l'utilità della sierologia per SARS-CoV-2 in pazienti con segni e/o sintomi compatibili con COVID-19 ma tampone nasofaringeo molecolare ripetutamente negativo. Durante il periodo di studio sono stati arruolati pazienti con segni e/o sintomi di COVID-19 e RT-PCR ripetutamente negativa ("probabili", n=20), pazienti con segni e/o sintomi compatibili con COVID-19 ma con una potenziale diagnosi alternativa ("sospetti", n=15), pazienti senza segni e/o sintomi compatibili con COVID-19 ("non sospetti"), pazienti con COVID-19 confermato alla RT-PCR ("confermati", n=40) e campioni pre-pandemia (n=55). Dallo studio emerge che i "probabili" , rispetto ai "certi", hanno sviluppato un simile tasso di sieropositività e simili livelli di IgG e IgM(60.0% vs 80.0% per le IgG, p-value = 0.13; 50.0% vs 72.5% per le IgM, p-value = 0.10), mentrehannosviluppato un tasso di sieropositivitànettamente superiore rispetto ai sospetti e ai non sospetti (60.0% vs 13.3% e 11.6% per le IgG; 50.0% vs 0% e 4.7% per le IgM; p-values < 0.01). Inoltre,

	N = 43), (iv) RT-PCR confirmed COVID-19 patients (N = 40), and (v) pre-pandemicsamples (N = 55). Results: Probables hadsimilarseropositivity and levels of IgG and IgMantibodies as propensity-score matched RT-PCR confirmed COVID-19 patients (60.0% vs 80.0% for IgG, p-value = 0.13; 50.0% vs 72.5% for IgM, p-value = 0.10), but multi-foldhigherseropositivity rates than Suspects and matched Non-suspects (60.0% vs 13.3% and 11.6% for IgG; 50.0% vs 0% and 4.7% for IgMrespectively; p-values < 0.01). However, Probables werehalf as likely to receive COVID-19 treatmentthan the RT-PCR confirmed COVID-19 patients withsimilardiseaseseverity. Conclusions: Findingsfromthisstudyindicate a high likelihood of acute COVID-19 among RT-PCR negativewithtypicalsigns/symptoms, but a common omission of COVID-19 therapiesamongthese patients. Clinicallydiagnosed COVID-19, independent of RT-PCR positivity, thus has a potential vital role in guidingtreatmentdecisions.	è da sottolinere come solo la metà dei « probabili » ha ricevutouna terapia specifica per COVID-19, a parità di severitàdellamalattia. I risultati di questo studio, malgrado la ridottanumerositàcampionaria, sottolineano come siaprincipalmente il datoclinico a doverguidare l'eventualeinizio di un trattamentospecifico, nel corso dellapandemia da SARS-CoV-2, specialmente in assenza di unaprobabilediagnosialternativa. Il rischio di impostare un trattamentospecifico solo in base al risultatodell'esamemolecolare per SARS-CoV-2 è infattiquello, in diversicasi, di perdere tempo e di far quindiprogredire la malattia verso glistadi più avanzati.

Jennifer Hammond et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 The New England Journal of Medicine https://www.nejm.org/doi/pdf/10.1056/NEJMoa2118542?articleTools=true	BACKGROUND Nirmatrelvir is an orally administered severe acute respiratory syndrome coronavirus 2 main protease (Mpro) inhibitor with potent pan–human-coronavirus activity in vitro. METHODS We conducted a phase 2–3 double-blind, randomized, controlled trial in which symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe coronavirus disease 2019 (Covid-19) were assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus 100 mg of ritonavir (a pharmacokinetic enhancer) or placebo every 12 hours for 5 days. Covid-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated. RESULTS A total of 2246 patients underwent randomization; 1120 patients received nirmatrelvir plus ritonavir (nirmatrelvirgroup) and 1126 received placebo (placebo group). In the planned interim analysis of patients treated within 3 days after symptom onset (modified intention-to treat population, comprising 774 of the 1361 patients in the full analysis population), the incidence of Covid-19–related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32	Trial di fase 2-3 in doppio cieco, randomizzato e controllato in cui adulti sintomatici, non vaccinati e non ospedalizzati, ad alto rischio di progressione verso una forma grave di Covid-19 sono stati assegnati in rapporto 1:1 a ricevere 300 mg di nirmatrelvir per via orale (inibitore della proteasi principale Mpro con una potente attività in vitro contro i coronavirus umani), più 100 mg di ritonavir o placebo. I risultati hanno mostrato che il trattamento di adulti con COVID-19 sintomatici con nirmatrelvirpiù ritonavir è associato ad unariduzione del rischio di progressione a COVID-19 severo dell'89% rispetto al gruppotrattato con placebo, con un buonprofilo di sicurezza.

	percentage points (95% confidence interval [CI], −9.04 to −3.59; P<0.001; relative risk reduction, 89.1%); the incidence was 0.77% (3 of 389 patients) in the nirmatrelvir group, with 0 deaths, as compared with 7.01% (27 of 385 patients) in the placebo group, with 7 deaths. Efficacy was maintained in the final analysis involving the 1379 patients in the modified intention-to-treat population, with a difference of −5.81 percentage points (95% CI, −7.78 to −3.84; P<0.001; relative risk reduction, 88.9%). All 13 deaths occurred in the placebo group. The viral load was lower with nirmaltrelvir plus ritonavir than with placebo at day 5 of treatment, with an adjusted mean difference of −0.868 log10 copies per milliliter when treatment was initiated within 3 days after the onset of symptoms. The incidence of adverse events that emerged during the treatment period was similar in the two groups (any adverse event, 22.6% with nirmatrelvir plus ritonavir vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%; and adverse events leading to discontinuation of the drugs or placebo, 2.1% vs. 4.2%). Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) occurred more frequently with nirmatrelvir plus ritonavir than with placebo. CONCLUSIONS Treatment of symptomatic Covid-19 with nirmatrelvir plus ritonavir resulted in a risk of progression to severe Covid-19 that was 89% lower than the risk with placebo, without evident safety concerns. (Supported by Pfizer;	

	ClinicalTrials.gov number, NCT04960202. opens in new tab.)	

Konig S. et al.; JAMA A Comparative Analysis of In-Hospital Mortality per Disease Groups in Germany Before and During the COVID-19 Pandemic From 2016 to 2020 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789056	**Importance** Throughout the ongoing SARS-CoV-2 pandemic, it has been critical to understand not only the viral disease itself but also its implications for the overall health care system. Reports about excess mortality in this regard have mostly focused on overall death counts during specific pandemic phases. **Objective** To investigate hospitalization rates and compare in-hospital mortality rates with absolute mortality incidences across a broad spectrum of diseases, comparing 2020 data with those of prepandemic years. **Design,** Retrospective, cross-sectional, multicentric analysis of administrative data from 5 821 757	

	inpatients admitted from January 1, 2016, to December 31, 2020, to 87 German Helios primary to tertiary care hospitals. **Exposures** Exposure to SARS-CoV-2. **Main Outcomes and Measures** Administrative data were analyzed from January 1, 2016, to March 31, 2021, as a consecutive sample for all inpatients. Disease groups were defined according to *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (*ICD-10*; German modification) encoded main discharge diagnoses. Incidence rate ratios (IRRs) for hospital admissions and hospital mortality counts, as well as relative mortality risks (RMRs) comparing 2016-2019 with 2020 (exposure to the SARS-CoV-2 pandemic), were calculated with Poisson regression with log-link function. **Results** Data were examined for 5 821 757 inpatients (mean [SD] age,	Studio cross-sectional analizzante i dati di quasi sei milioni di pazienti ricoverati, tra gennaio 2016 e dicembre 2020 in 87 ospedali tedeschi, al fine di identificare un eventuale eccesso di mortalità patologia-specifico intercorso con l'arrivo della pandemia. In termini di incidenza, il 2020, se paragonato agli anni 2016-1029, si è caratterizzato da un aumento delle diagnosi di malattie respiratorie, affiancato da una riduzione dell'incidenza di patologie di altra natura. Tuttavia, una volta esclusi i pazienti COVID dall'analisi, la mortalità nel 2020 è risultata inferiore sia per l'intera coorte che nel sottogruppo delle patologie respiratorie.

	56.4 [25.3] years; 51.5% women), including 125 807 in-hospital deaths. Incidence rate ratios for hospital admissions were associated with a significant reduction for all investigated disease groups (IRR, 0.82; 95% CI, 0.79-0.86; *P*<.001). After adjusting for age, sex, the Elixhauser Comorbidity Index score, and SARS-CoV-2 infections, RMRs were associated with an increase in infectious diseases (RMR, 1.28; 95% CI, 1.21-1.34; *P*<.001), musculoskeletal diseases (RMR, 1.19; 95% CI, 1.04-1.36; *P*=.009), and respiratory diseases (RMR, 1.09; 95% CI, 1.05-1.14; *P*<.001) but not for the total cohort (RMR, 1.00; 95% CI, 0.99-1.02; *P*=.66). Regarding in-hospital mortality, IRR was associated with an increase within the *ICD-10* chapter of respiratory diseases (IRR, 1.28; 95% CI, 1.13-1.46; *P*<.001) in comparing 2020 with 2016-2019, in contrast to being associated with a reduction in IRRs for the overall cohort and several other subgroups. After exclusion of	

	patients with SARS-CoV-2 infections, IRRs were associated with a reduction in absolute in-hospital mortality for the overall cohort (IRR, 0.78; 95% CI, 0.72-0.84; *P*<.001) and the subgroup of respiratory diseases (IRR, 0.83; 95% CI, 0.74-0.92; *P*<.001). Conclusions and Relevance This cross-sectional study of inpatients from a multicentric German database suggests that absolute in-hospital mortality for 2020 across disease groups was not higher compared with previous years. Higher IRRs of in-hospital deaths observed in patients with respiratory diseases were likely associated with individuals with SARS-CoV-2 infections.	