DALLA CLINICA AL DATABASE: ESPERIENZA DEL DIPARTIMENTO DI MALATTIE INFETTIVE DELL'OSPEDALE SACCO

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ASST Fatebenefratelli Sacco

Disclosures

- AG received consultancy fees from Mylan and educational and gra
  support from Gilead

data base

Vocabolario on line

data base ‹*dèitë bèis*› (o ***database***) locuz. ingl. (propr. «base di dati»; pl. *data bases* ‹... *bèisi*ʃ›), usata in ital. come s. m. (e comunem. pronunciata ‹*dàta bèis*›). – Archivio elettronico di dati correlati, registrati nella memoria di un computer e organizzati in modo da poter essere facilmente, rapidamente e selettivamente rintracciabili uno per uno, oppure per gruppi determinati, mediante appositi programmi di gestione e di ricerca (chiamati anch'essi *data base*, ma più propr. denominati *data base management system*, in sigla *DBMS*).

SINONIMI E CONTRARI

data base

data base /'deitə 'beis/, it. /'d
ingl., usato in ital. al masch.
[raccolta di dati registrati ne
del computer, passibili di int
≈ banca dati, base di dati.

Sistema Socio Sanitario

Regione Lombardia

ASST Fatebenefratelli Sacco

DELIBERAZIONE DEL DIRETTORE GENERALE n. 380 del 27 MAR. 2020

OGGETTO: Autorizzazione allo studio no profit, osservazionale, dal titolo "Registro delle infezioni sospette e accertate COVID-19", protocollo COVID-19, da svolgersi presso il Dipartimento Malattie Infettive della ASST Fatebenefratelli Sacco, diretto dal Dott. Giuliano Rizzardini.

Dati raccolti

Demografiche

Età
Genere
Peso e altezza
Residenza
Nazionalità

Cliniche

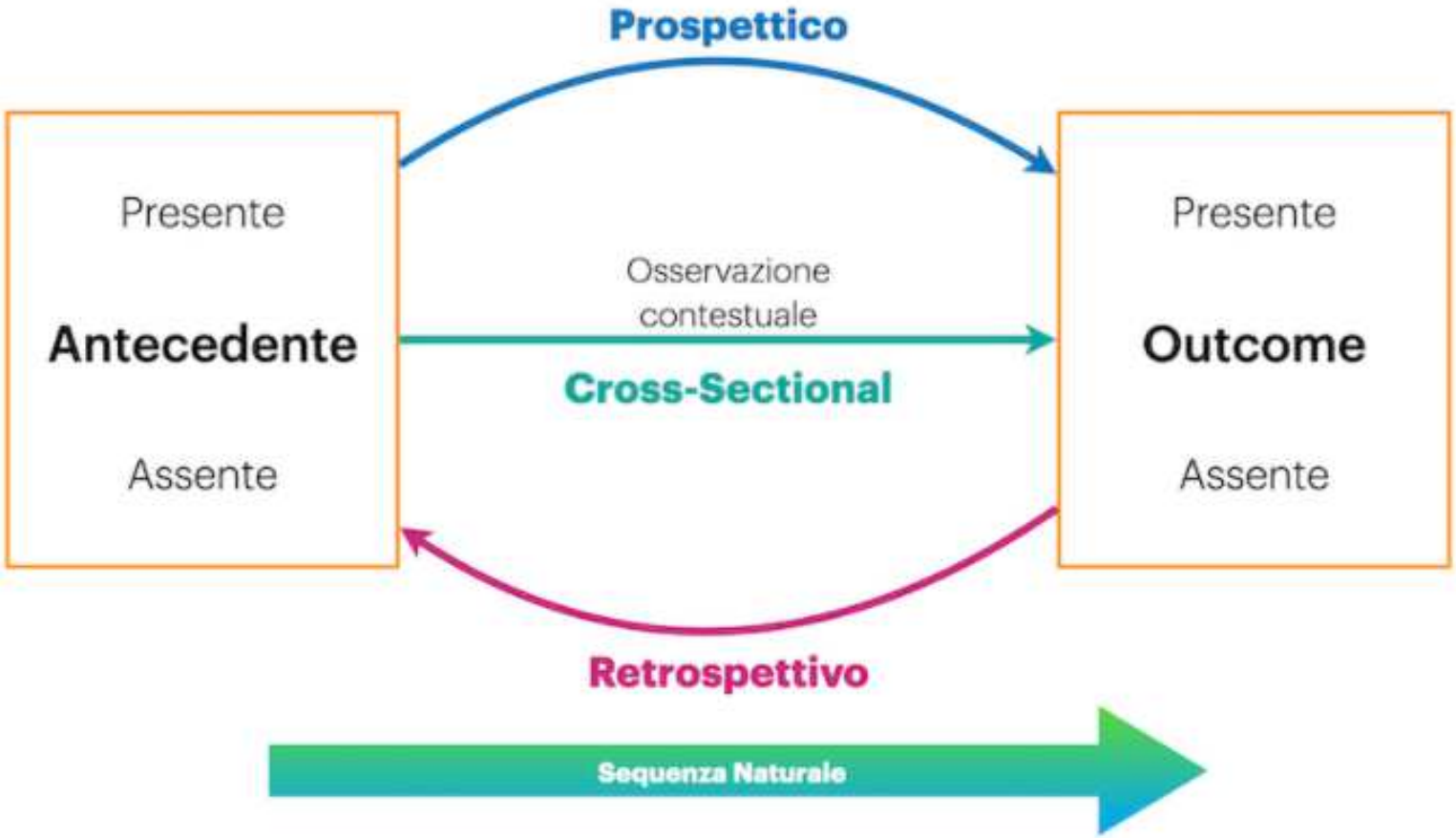
Sintomi di esordio
Data esordio sintomi
Esami ematochimici
Accertamenti microbiologici
Emogas analisi
Radiologia
Outcome

Terapie

O2 terapia
Ventilazione non-invasiva
Ventilazione invasiva
Terapie antivirali
Terapia steroidea
Antibiotici
Anticoagulanti
Terapie concomitanti

Tipologia di studi consentiti da database che raccoglie prospetticamente i dati

- **Studio** di coorte
  - **Studio** di coorte prospettico
  - **Studio** di coorte retrospettivo (i.e. caso-controllo)
- **Studio osservazionale** trasversale o cross sectional.



Scegliere il tipo di studio osservazionale

Outcome valutabili

- Sintomatologia
- Mortalità
- Dimissione
- Massimo supporto O2
- Tempo in O2

Comment › Clin Infect Dis. 2020 Jul 28;71(15):889-890. doi: 10.1093/cid/ciaa330.

Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study

Andrea Giacomelli [1 2], Laura Pezzati [1 2], Federico Conti [1 2], Dario Bernacchia [1 2], Matteo Siano [1 2], Letizia Oreni [1], Stefano Rusconi [1 2], Cristina Gervasoni [1], Anna Lisa Ridolfo [1], Giuliano Rizzardini [3 4], Spinello Antinori [1 2], Massimo Galli [1 2]

Affiliations + expand

PMID: 32215618 PMCID: PMC7184514 DOI: 10.1093/cid/ciaa330

Free PMC article

Table 1. Characteristics of Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection Assessed for Taste and Olfactory Disorders (N = 59)

Patients	No. (%)
Age, y, median (IQR)	60 (50–74)
Male sex	40 (67.8)
Days from illness onset to hospital admission, median (IQR)	6 (4–10)
Days from illness onset to the interview, median (IQR)	15 (10–21)
Pneumonia at hospital admission	43 (72.8)
Symptoms at hospital admission	
Fever	43 (72.8)
Cough	22 (37.3)
Dyspnea	15 (25.4)
Sore throat	1 (1.7)
Arthralgia	3 (5.1)
Coryza	1 (1.7)
Headache	2 (3.4)
Asthenia	1 (1.7)
Abdominal symptoms	5 (8.5)
No taste or olfactory disorders	39 (66.1)
With olfactory and/or taste disorders	20 (33.9)
Taste disorders only	
Dysgeusia	5 (8.5)
Ageusia	1 (1.7)
Olfactory disorders only	
Hyposmia	3 (5.1)
Anosmia	0 (0)
Mixed taste and olfactory disorders	
Dysgeusia and hyposmia	2 (3.4)
Dysgeusia and anosmia	2 (3.4)
Ageusia and hyposmia	2 (3.4)
Ageusia and anosmia	5 (8.5)

Pharmacological Research 158 (2020) 104931

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: A prospective cohort study

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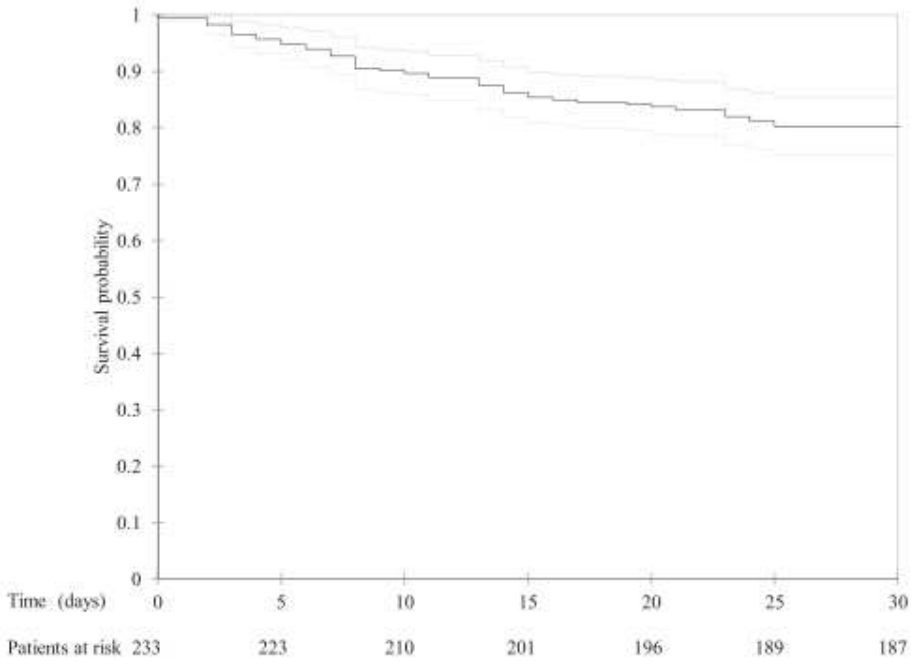

Fig. 1. Kaplan-Meier curve of the probability of survival over time in patients with SARS-CoV-2 infection hospitalised in Milan, Italy. The continuous line represents the estimated survival curve, and the dashed lines the upper and lower limits of the 95 % confidence interval.

Table 1
Characteristics upon hospital admission of the COVID-19 patients who or died during the study period.

Characteristic	Total (n = 233)	Survivors (n = 185)	Non-survivors (n = 48)	P
Gender, n (%)	161 (69.1)	122 (65.9)	39 (81.2)	0.053
Male	72 (30.9)	63 (34.1)	9 (18.8)	
Female				
Age in years, n (%)				
18 – 25	2 (0.9)	2 (1.1)	0 (0.0)	*<0.001*
26 – 35	16 (6.9)	16 (8.6)	0 (0.0)	
36 – 45	23 (9.9)	22 (11.9)	1 (2.1)	
46 – 55	37 (15.9)	35 (18.9)	2 (4.2)	
56 – 65	56 (24.0)	45 (24.3)	11 (22.9)	
66 – 75	55 (23.6)	36 (19.5)	19 (39.6)	
76 – 85	34 (14.6)	24 (13.0)	10 (20.8)	
86 – 95	10 (4.3)	5 (2.7)	5 (10.4)	
Transferred from other hospitals, n (%)	98 (42.1)	68 (36.8)	30 (62.5)	*0.002*
Median time from onset of illness (IQR), days	7 (4 – 9)	6 (4 – 9)	7 (4 – 9)	0.970
Symptoms, n (%)				
Cough	121 (51.9)	99 (53.5)	22 (45.8)	0.418
Dyspnea	82 (35.2)	67 (36.2)	15 (31.2)	0.612
Sore throat	11 (4.7)	11 (5.9)	0 (0.0)	0.126
Arthralgia/myalgia	12 (5.2)	11 (5.9)	1 (2.1)	0.468
Headache	12 (5.2)	12 (6.5)	0 (0.0)	0.134
Asthenia	28 (12.0)	21 (11.4)	7 (14.6)	0.618
Vomiting and/or diarrhea	24 (10.3)	22 (11.9)	2 (4.2)	0.180
Signs, n (%) or median (IQR)				
Fever >37.3 °C	156 (67.0)	125 (67.6)	31 (64.6)	0.732
Body temperature (°C)	38 (37.3 – 38.6)	38.0 (37.2 – 38.6)	38.0 (37.4 – 38.4)	0.903
Systolic blood pressure, mm Hg	125 (118 – 140)	125 (119 – 140)	130 (117 – 150)	0.421
Diastolic blood pressure, mm Hg	75 (70 – 80)	75 (70 – 80)	75 (62.5 – 87.5)	0.881
Pulse, beats per minute	86 (76 – 100)	86 (77 – 100)	83 (75 – 100)	0.806
Respiratory rate, breaths per minute	21 (18 – 28)	20 (18 – 26)	24 (20 – 30)	*0.009*
Percutaneous oxygen saturation, %	95 (93 – 97)	95 (93 – 97)	94.5 (90 – 97)	0.169
X-ray signs of lung changes, n (%)				
No alterations	32 (13.7)	30 (16.2)	2 (4.2)	0.033
Interstitial changes	119 (51.1)	100 (54.1)	19 (39.6)	0.078
Monolateral consolidation(s)	139 (59.7)	115 (62.2)	24 (50.0)	0.139
Bilateral consolidation(s)	85 (36.5)	71 (38.4)	14 (29.2)	0.313
Pleural effusion	17 (7.3)	11 (5.9)	6 (12.5)	0.127
Oxygen therapy, n (%)				
No	96 (41.2)	89 (48.1)	7 (14.6)	*<0.0001*
Simple face mask	49 (21.0)	35 (18.9)	14 (29.2)	
Venturi-type oxygen mask	36 (15.5)	31 (16.8)	5 (10.4)	
Face mask with oxygen reservoir bag	15 (6.4)	10 (5.4)	5 (10.4)	
Continuous positive airway pressure (cPAP)	29 (12.4)	19 (10.3)	10 (20.8)	
Mechanical ventilation	8 (3.4)	1 (0.5)	7 (14.6)	
Disease severity[†], n (%)				
Mild	32 (13.7)	30 (16.2)	2 (4.2)	*<0.001*
Moderate	113 (48.5)	94 (50.8)	19 (39.6)	
Severe	80 (34.3)	60 (32.4)	20 (41.7)	
Critical	8 (3.4)	1 (0.5)	7 (14.6)	

Table 3
Cox regression analysis of the demographic and clinical factors associated with SARS-CoV-2 infection mortality.

Characteristic	HR	95 % CI	P	aHR	95 % CI	P
Gender						
Female	1			1		
Male	2.02	0.98 – 4.16	0.058	1.42	0.62 – 3.28	0.409
Age	1.81	1.44 – 2.28	*< 0.0001*	2.08	1.48 – 2.92	*< 0.000*
Per 10 years more						
Age unadjusted Charlson comorbidity index	1.32	1.12 – 1.57	*0.001*	1.07	0.83 – 1.37	*0.605*
Per one point more						
Obesity[¥]						
No	1			1		
Yes	2.01	1.07 – 3.81	*0.031*	3.04	1.42 – 6.49	*0.004*
Being treated with at least one anti-hypertensive agent						
No	1			1		
Yes	2.78	1.56 – 4.94	*< 0.001*	1.41	0.73 – 2.74	0.309
Disease severity[¥]						
Mild	1			1		
Moderate	2.82	0.66 – 12.10	0.163	1.30	0.29 – 5.77	0.727
Severe	4.43	1.04 – 18.97	*0.045*	1.50	0.32 – 7.04	0.605
Critical	35.35	7.29 – 171.43	*< 0.0001*	8.26	1.41 – 48.29	*0.019*
Presence of anemia[¥]						
No	1			1		
Yes	2.43	1.33 – 4.43	*0.004*	1.31	0.67 – 2.59	0.429
Lymphocyte count	0.91	0.00 – 0.97	*0.008*	0.98	0.91 – 1.06	0.664
Per 100 cells/μL more						
D-dimer						
≤ 1000 μg/L	1			1		
> 1000 μg/L	2.70	1.45 – 5.02	*0.002*	1.13	0.57 – 2.23	0.725
C-reactive protein	1.26	1.15 – 1.38	*< 0.0001*	1.17	1.02 – 1.35	*0.028*
Per 50 mg/L more						
Creatinine,	1.08	1.01 – 1.15	*0.030*	1.0	0.92 – 1.1	0.528
Per 0.5 mg/dL more						
Creatine kinase						
≤ 185 U/L	1			1		
> 185 U/L	3.26	1.84 – 5.75	*< 0.001*	2.58	1.37 – 4.87	*0.003*

Received: 19 January 2021 | Revised: 8 March 2021 | Accepted: 9 March 2021
DOI: 10.1002/jmv.26933

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Impact of gender on patients hospitalized for SARS-COV-2 infection: A prospective observational study

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Abstract

Biological sex could affect the natural history of severe acute respiratory syndrome coronavirus 2 infection. We enrolled all COVID-19 patients admitted to two COVID-19 hospitals in Milan in a prospective observational study. The primary outcome was death during the study period and the secondary outcome was critical disease at hospital admission. The association(s) between clinically relevant, noncollinear variables, and the primary outcome was assessed with uni- and multivariable Logistic regression models. A total of 520 patients were hospitalized of whom 349 (67%) were males with a median age 61 (interquartile range: 50–72). A higher proportion of males presented critically ill when compared to females (30.1% vs. 18.7%, $p < .046$). Death occurred in 86 (24.6%) males and 27 (15.8%) females ($p = .024$). In multivariable analysis age (per 10 years more) (adjusted odds ratio [AOR]: 1.83 [95% confidence interval [CI]: 1.42–2.35], $p < .0001$), obesity (AOR: 2.17 [95% CI: 1.10–4.31], $p = .026$), critical disease at hospital admission (AOR 6.34 [95% CI: 3.50–11.48], $p < .0001$) were independently associated to higher odds of death whereas gender was not. In conclusion, a higher proportion of males presented critically ill at hospital admission. Age, critical disease at hospital admission, obesity, anemia, D-dimer, estimated glomerular filtration rate, lactate dehydrogenase, and creatine kinase predicted death in hospitalized COVID-19 patients.

TABLE 1 Characteristics of the study population at hospital admission

Characteristics	Total (*n* = 520)	Female: 171 (33%)	Male: 349 (67%)
Age in years, median (IQR)	61 [50, 72]	61 [49, 73]	61 [50, 71]
Chronic conditions			
Respiratory diseases, *n* (%)	78 (15.0)	29 (17.0)	49 (14.0)
Cardiovascular diseases, *n* (%)	254 (48.8)	79 (46.2)	175 (50.1)
Diabetes, *n* (%)	61 (11.7)	16 (9.4)	45 (12.9)
Kidney diseases, *n* (%)	42 (8.1)	11 (6.4)	31 (8.9)
Oncological diseases, *n* (%)	50 (9.6)	20 (11.7)	30 (8.6)
Immune system disorders, *n* (%)	39 (7.5)	16 (9.4)	23 (6.6)
Liver diseases, *n* (%)	11 (2.1)	2 (1.2)	9 (2.6)
Obesity, *n* (%)	92 (17.7)	23 (13.5)	69 (19.8)
Influenza vaccination (%)			
YES	109 (21.0)	36 (21.1)	73 (20.9)
NO	319 (61.3)	110 (64.3)	209 (59.9)
nn	92 (17.7)	25 (14.6)	67 (19.2)
Median time from onset of illness (IQR), days	8 (4, 11)	8 (4, 11)	8 (4, 10)
Symptoms, *n* (%)			
Cough (%)	271 (52.1)	91 (53.2)	180 (51.6)
Dyspnea (%)	225 (43.3)	67 (39.2)	158 (45.3)
Sore throat (%)	26 (5.0)	11 (6.4)	15 (4.3)
Artrhralgia/Myalgia (%)	29 (5.6)	6 (3.5)	23 (6.6)
Headache (%)	25 (4.8)	8 (4.7)	17 (4.9)
Asthenia (%)	62 (11.9)	17 (9.9)	45 (12.9)
Vomiting and/or diarrhea (%)	72 (13.8)	33 (19.3)	39 (11.2)
Fever (>37.3°C) (%)	324 (62.3)	88 (51.5)	236 (67.6)
Disease severity, *n* (%)			
Mild	40 (7.7)	14 (8.2)	26 (7.4)
Moderate	226 (43.5)	80 (46.8)	146 (41.8)
Severe	117 (22.5)	45 (26.3)	72 (20.6)
Critically	137 (26.3)	32 (18.7)	105 (30.1)

Drugs & Aging
https://doi.org/10.1007/s40266-020-00812-8

ORIGINAL RESEARCH ARTICLE

Drug–Drug Interactions and Prescription Appropriateness in Patients with COVID-19: A Retrospective Analysis from a Reference Hospital in Northern Italy

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Accepted: 21 October 2020

Abstract

Background Patients hospitalised with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; coronavirus 2019 disease (COVID-19)] infection are frequently older with co-morbidities and receiving polypharmacy, all of which are known risk factors for drug–drug interactions (DDIs). The pharmacological burden may be further aggravated by the addition of treatments for COVID-19.

Objective The aim of this study was to assess the risk of potential DDIs upon admission and during hospitalisation in patients with COVID-19 treated at our hospital.

Methods We retrospectively analysed 502 patients with COVID-19 (mean age 61 ± 16 years, range 15–99) treated at our hospital with a proven diagnosis of SARS-CoV-2 infection hospitalised between 21 February and 30 April 2020 and treated with at least two drugs.

Results Overall, 68% of our patients with COVID-19 were exposed to at least one potential DDI, and 55% were exposed to at least one potentially severe DDI. The proportion of patients experiencing potentially severe DDIs increased from 22% upon admission to 80% during hospitalisation. Furosemide, amiodarone and quetiapine were the main drivers of potentially severe DDIs upon admission, and hydroxychloroquine and particularly lopinavir/ritonavir were the main drivers during hospitalisation. The majority of potentially severe DDIs carried an increased risk of cardiotoxicity. No potentially severe DDIs were identified in relation to tocilizumab and remdesivir.

Conclusions Among hospitalised patients with COVID-19, concomitant treatment with lopinavir/ritonavir and hydroxychloroquine led to a dramatic increase in the number of potentially severe DDIs. Given the high risk of cardiotoxicity and the scant and conflicting data concerning their efficacy in treating SARS-CoV-2 infection, the use of lopinavir/ritonavir and hydroxychloroquine in patients with COVID-19 with polypharmacy needs to be carefully considered.

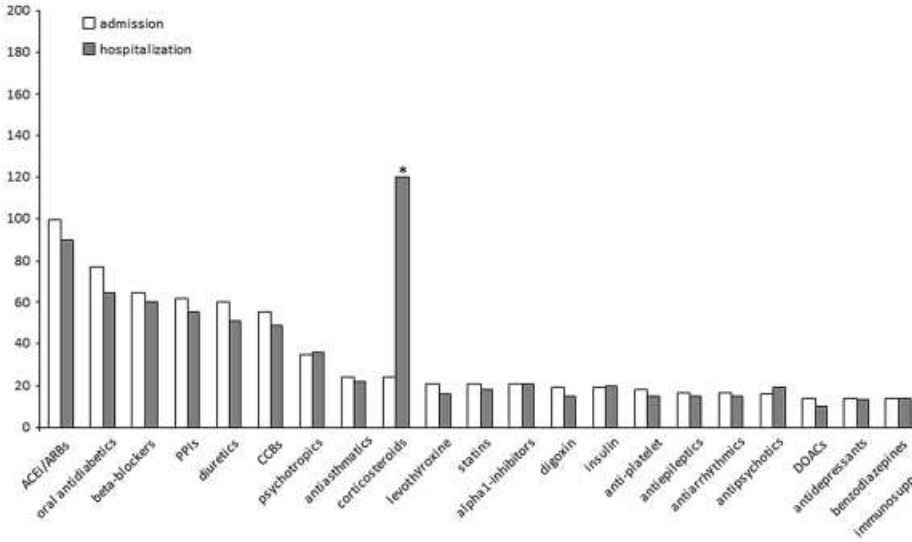

Fig. 1 Distribution of the main drug classes present upon admission and during hospitalisation (data are given as absolute numbers). *ACEi* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin-receptor blockers, *CCBs* calcium channel blockers, *DOAC* anticoagulants, *PPIs* proton pump inhibitors. *$p < 0$

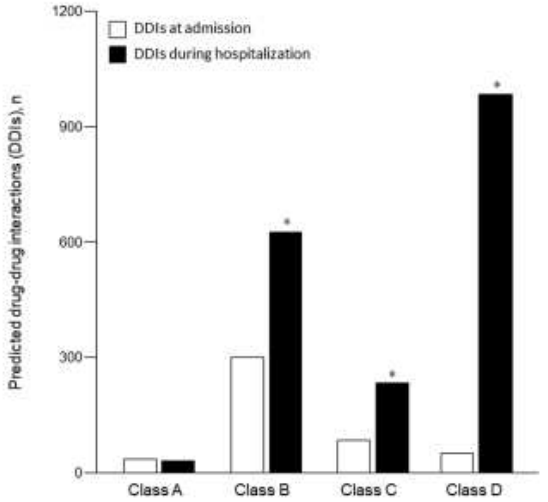

Fig. 2 Distribution of predicted DDIs upon admission and during hospitalisation. Class A: minor (clinically irrelevant interaction); class B: moderate (interaction associated with an uncertain or variable event); class C: major (interaction associated with a serious event that can be managed); and class D: contraindicated or very severe (interaction potentially associated with a serious event; co-administration should be avoided or careful monitoring established). *$p < 0.01$ vs. admission

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-021-01604-6

BRIEF REPORT

Risks of potential drug–drug interactions in COVID-19 patients treated with corticosteroids: a single-center experience

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Received: 16 April 2021 / Accepted: 22 May 2021

Table 2 Potential class B drug–drug interactions ($n=756$) in hospitalized COVID-19 patients treated with corticosteroids ($n=471$)

Potential adverse event/interacting agents	*N* (%)
Antagonism of the action of antihypertensive drugs	267 (35%)
Beta-blockers	110
ACE inhibitors	82
Angiotensin II receptor antagonists	50
Alpha 1 blockers	15
Calcium channel blockers	7
Diuretics	3
Hypokalemia (lethargy, asthenia, arrhythmias)	139 (18%)
Diuretics	105
Beta agonists	34
Bleeding	130 (17%)
Acetylsalicylic acid	116
Vitamin K inhibitors	14
Reduced exposure and efficacy of remdesivir	97 (13%)
Reduced exposure and efficacy of hypoglycemic agents	81 (11%)
Metformin	65
Glinides	9
Incretin mimetics	7
Increased risk of tendon rupture	15 (2%)
Fluoroquinolones	15
Others	27 (4%)
Quetiapine	16
Antiepileptic drugs	6
Others	5

Table 1 Potential class C drug–drug interactions ($n=25$) in hospitalized COVID-19 patients treated with corticosteroids ($n=471$)

Potential adverse event	Interacting agent
Reduction of the exposure and efficacy of caspofungin	Caspofungin
Reduction of the exposure and efficacy of voriconazole	Voriconazole
Increased risk of infections	Adalimumab
Increased risk of gastrointestinal adverse effects	Deferasirox
Reduction of exposure to efavirenz and/or corticosteroids	Efavirenz
Increased risk of gastrointestinal adverse effects	Ketorolac

Received: 16 June 2020 | Accepted: 3 August 2020
DOI: 10.1002/jmv.26407

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: A retrospective cohort study

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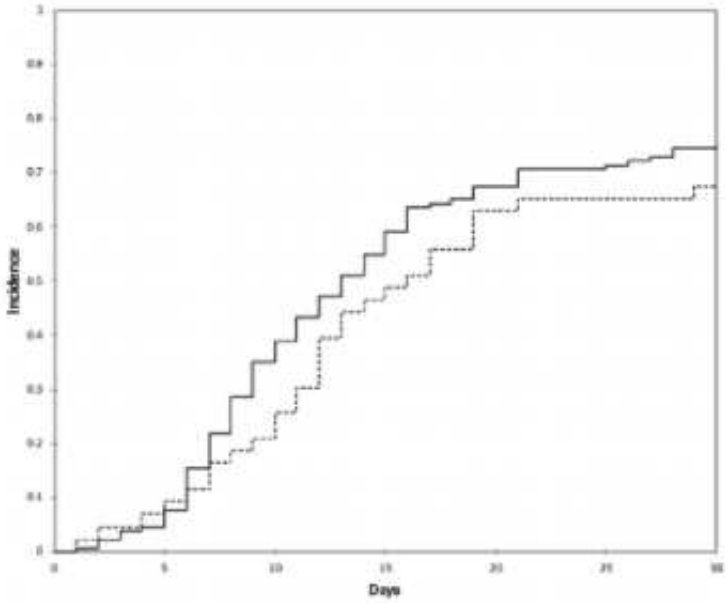

FIGURE 2 Cumulative incidence of improvement in the early treatment (ET) group (dashed line) vs delayed treatment (DT) group (solid line)

TABLE 1 Baseline characteristics of the study population at LPV/r + HCQ initiation

Characteristic	Total (n = 172)	Early treatment (n = 43)	Delayed treatment (n = 129)	P
Gender, n (%)				
Male	124 (72.1)	29 (67.4)	95 (73.6)	.556
Female	48 (27.7)	14 (32.6)	34 (26.4)	
Age, median (IQR)	61.7 (50.9-72.7)	64.9 (55.0-78.0)	61.7 (50.2-72.3)	.110
BMI > 30, n (%)	28 (16.3)	7 (16.3)	21 (16.3)	.999
Charlson comorbidity index[a], median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	.077
Symptoms, n (%)				
Cough	93 (35.4)	17 (39.5)	76 (58.9)	.034
Dyspnea	61 (35.4)	17 (39.5)	44 (34.1)	.582
Sore throat	6 (3.5)	0 (0.0)	6 (4.6)	.338
Arthralgia/myalgia	6 (3.5)	1 (2.3)	5 (3.9)	.999
Headache	9 (5.2)	5 (11.6)	4 (3.1)	.044
Asthenia	21 (12.2)	6 (13.9)	15 (11.6)	.788
Vomiting and/or diarrhea	19 (11.0)	3 (6.9)	16 (12.4)	.410
Fever > 37.3°C	126 (72.7)	26 (60.4)	100 (76.7)	.045
Disease severity,[b] n (%)				
Mild	14 (8.1)	7 (16.3)	7 (5.42)	.125
Moderate	92 (53.4)	19 (44.2)	73 (56.6)	
Severe	60 (34.9)	16 (37.2)	44 (38.1)	
Critical	6 (3.5)	1 (7.7)	5 (3.9)	
Laboratory tests, median value (IQR)				
White blood cells, $\times 10^9$/L	5.73 (4.3-7.7)	4.7 (4.4-7.2)	5.8 (4.5-7.9)	.017
Lymphocytes, $\times 10^9$/L	0.97 (0.71-1.22)	0.92 (0.76-1.22)	0.98 (0.71-1.23)	.505
Neutrophils, $\times 10^9$/L	4.1 (2.9-6.4)	3.2 (2.5-5.6)	4.3 (3.1-6.5)	.030
Hemoglobin, g/dL	13.8 (12.8-14.8)	13.7 (12.6-14.4)	13.9 (12.8-15.0)	.104
Platelets, $\times 10^9$/L	176 (137-221)	176 (135-207)	177 (141-229)	.422
D-dimer, µg/L	926 (585-2054)	929 (590-2145)	926 (577-2037)	.978
PaO_2, mm Hg (n = 136)	70 (61-80)	77 (69-84)	67 (59-75)	<.001
C-reactive protein, mg/L	51.6 (24.3-122)	35.6 (19.0-95.3)	58.8 (31.6-140.8)	.045
Creatinine, mg/dL	0.96 (0.80-1.14)	0.90 (0.76-1.10)	0.99 (0.80-1.14)	.234
Lactate dehydrogenase, U/L	350 (269-452)	321 (243-448)	358 (277-450)	.160
Creatine kinase, U/L	111 (64-249)	109 (74-184)	113 (61-273)	.255
ALT, U/L	32 (20-55)	32 (20-57)	32 (21-55)	.717
Bilirubin, mg/dL	1.19 (1.05-1.21)	1.19 (0.94-1.20)	1.2 (1.10-1.23)	.049
Albumin, g/L	29 (26-32)	29 (26-32)	29 (26-32)	.718

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; IQR, interquartile range; n, number.
[a]Unadjusted for age.
[b]Disease severity classification proposed by Wu et al.[19]

Pharmacological Research 170 (2021) 105711

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Letter to the Editor

Remdesivir in moderate to severe COVID-19: A matter of time?

Cecilia Bonazzetti [1], Andrea Giacomelli [2], Martina Pavia [3], Chiara Fusetti [2], Martina Gerbi [2], Francesco Petri [2], Andrea Poloni [2], Letizia Oreni [4], Anna Lisa Ridolfo [4], Spinello Antinori [2]

Table 1
Characteristics of patients treated with remdesivir according to being exposed to remdesivir within one day from oxygen requirement or thereafter.

	Overall n = 87	Time from O2 to remdesivir start ≤ 1 day n = 27	Time from O2 to remdesivir start > 1 day n = 60	*p*
Age, median (IQR)	67.7 [56.1–77.7]	67.7 [55.2–81.7]	67.4 [56.6–75]	0.650
Biological sex, n (%)				
Female	19 (21.8)	9 (33.3)	10 (16.7)	0.098
Male	68 (78.2)	18 (66.7)	50 (83.3)	
Comorbidities, n (%)				
Obesity	21 (24.1)	7 (25.9)	14 (23.3)	0.792
Diabetes	16 (18.4)	4 (14.8)	12 (20.0)	0.766
Lung diseases	19 (21.8)	7 (25.9)	12 (20.0)	0.581
Heart diseases	49 (56.3)	12 (44.4)	37 (61.7)	0.164
Metabolic disorders	32 (36.8)	9 (33.3)	23 (38.3)	0.811
Renal diseases	6 (6.9)	1 (3.7)	5 (8.3)	0.661
Oncological diseases	14 (16.1)	3 (11.1)	11 (18.3)	0.535
Immune system disorders	6 (6.9)	1 (3.7)	5 (8.3)	0.661
Liver diseases	5 (5.7)	1 (3.7)	4 (6.7)	0.999
Number of comorbidities, n (%)	23 (26.4)	10 (37.0)	13 (21.7)	0.476
0	21 (24.1)	5 (18.5)	16 (26.7)	
1	26 (29.9)	8 (29.6)	18 (30.0)	
2	17 (19.5)	4 (14.8)	13 (21.7)	
3+				
Time from symptoms onset, median (IQR)	6.0 [4.0, 8.0]	7.0 [5.5–8.0]	6.0 [4.0–7.0]	0.160
Disease severity (%)				0.161
Moderate	35 (40.2)	14 (51.9)	21 (35.0)	
Severe	52 (59.8)	13 (48.1)	39 (65.0)	

List of abbreviations: n, number; IQR, Inter Quartile Range.

The primary outcome of interest was composite: non-inva
ventilation or invasive ventilation or death whichever occ
first.

Patients treated within one day from oxygen support s
frequently required non-invasive ventilation when com
those who started the drug after one day (11% vs 45%; p
whereas no significant differences were observed in
invasive ventilation requirement (7.4% vs 10%; p = 0
death (11.1% vs 18.3%; p = 0.535). The protocol defined
occurred less frequently in subjects exposed to remdesiv
one day from oxygen support start when compared to th
started the drug after one day [Hazard Ratio (HR): 0.
Confidence Interval (CI)) 0.00–0.86; p = *0.023*]. After
into the multivariable Cox model for age, biological sex, ti
symptoms onset and obesity the start of remdesivir wi
day from oxygen support start confirmed to be associa
reduced probability of occurrence of the protocol
outcome [adjusted HR: 0.36 (95% CI 0.00–0.96); *p = 0.041*

J Antimicrob Chemother
doi:10.1093/jac/dkab033

Comment on: Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU

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Sir,

We read with great interest the paper by Pasquini *et al.*[1] supporting the effectiveness of remdesivir in improving the survival of critically ill patients with COVID-19. However, we think that the results obtained by the authors need to be interpreted cautiously because of their possible serious biases.

The study included 51 patients of whom 25 received remdesivir a median of 7 days (IQR = 4–8 days) after ICU admission (the treatment group) and 26 who did not receive the drug (the control group). We wonder how many of the critically ill patients in the treatment group died before starting remdesivir and how they were considered in the analysis.

The possibility that a critical patient assigned to an experimental treatment may die pending the availability of the drug is not to be overlooked. In our clinical centre, which (to the best of our knowledge) was the first Italian centre to have access to the compassionate use of remdesivir,[2] 69 ICU patients were considered eligible for the treatment between 23 February and 20 March 2020, but 9 (13%) did not actually start the drug because a rapid and severe deterioration in their general condition led to their deaths.

If the patients who died within the 4–8 days before remdesivir became available in the study by Pasquini *et al.*[1] were included in the control group, an immortal time bias may have affected the final results and given a spurious survival advantage to the treated group.

Immortal time bias can arise when the period between cohort entry and the date of first exposure to a drug is not accounted for in the analysis.[3,4] In this specific case, the selection of the treated and untreated groups was based on an event (treatment with remdesivir) that followed the participants' study entry (time zero: ICU admission). This time lag is called 'immortal' because the subjects who end up in the treatment group have to be alive until the start of treatment, otherwise they would fall into the untreated group, and this could distort the observed effects and generate an illusion of treatment effectiveness.

Immortal time bias can be prevented by aligning assignment to the treatment or non-treatment groups with time zero. If this cannot be done, time-dependent analyses can be used to reduce the impact of the bias.[5]

Furthermore, we think it is questionable to exclude the SOFA score from variables included in the multivariate analysis of factors associated with mortality because there was a significant between-group difference in the score at the time of admission and it is well known that this clinical parameter provides valuable prognostic information in the case of patients admitted to an ICU.

Acknowledgements

We would like to thank all of the patients and their families and all of the medical staff (paramedics, nurses, physicians and students) who are making every effort to ensure the best care for patients suffering from COVID-19.

Transparency declarations

A.G. has received consultancy fees from Mylan and non-financial educational support from Gilead. S.A. has received support for research activities from Pfizer and Merck Sharp & Dome. All other authors: none to declare.

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JAMA Guide to Statistics and Methods

February 16, 2021

Immortal Time Bias in Observational Studies

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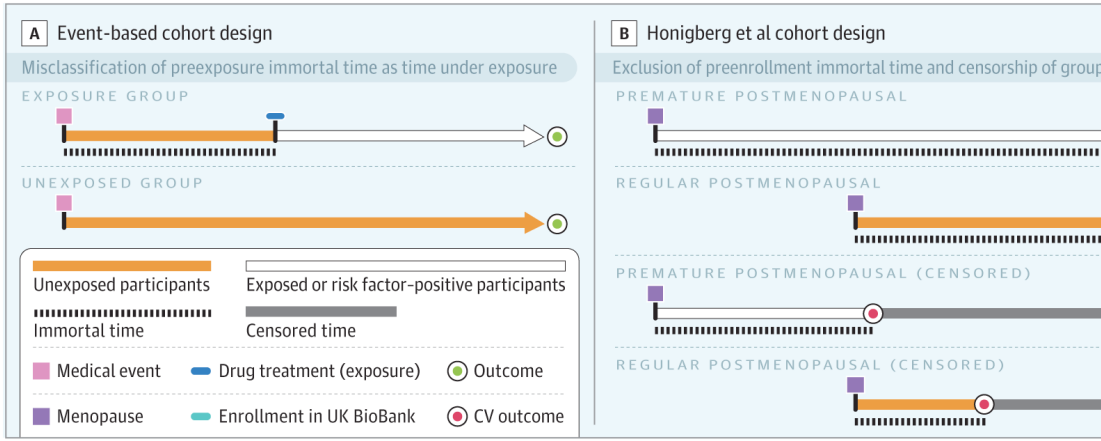
Author Affiliations | Article Information

JAMA. 2021;325(7):686-687. doi:10.1001/jama.2020.9151



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Platform Trials — Beware the Noncomparable Control Group

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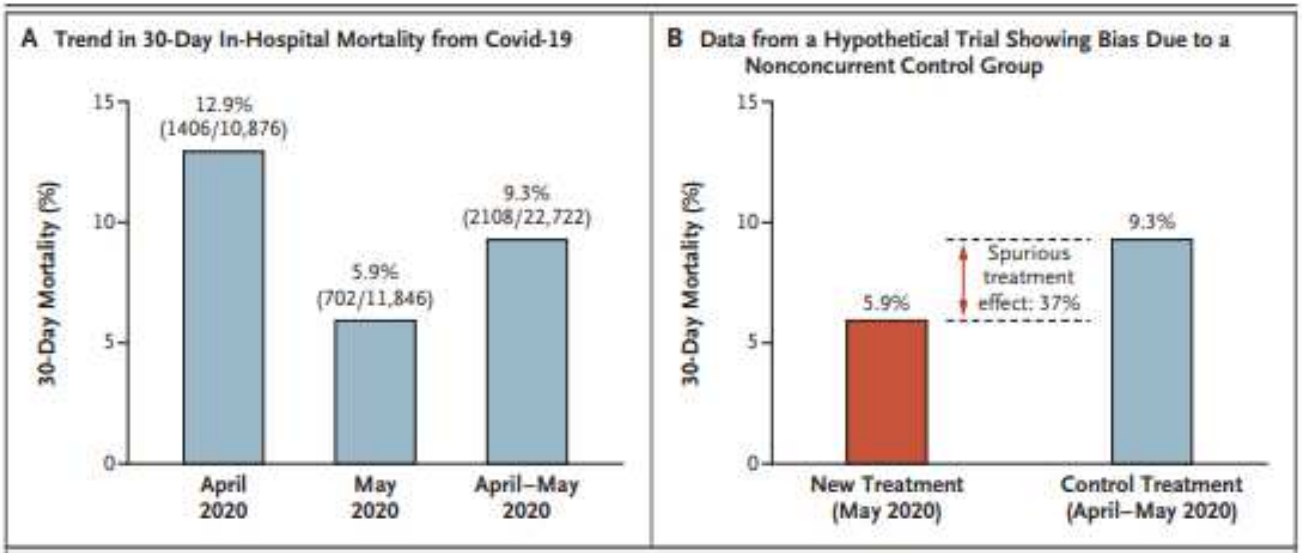

Figure 1. Hypothetical Example of How Nonconcurrent Randomization Could Bias the Results of a Trial.

Panel A shows the 30-day in-hospital mortality from Covid-19 in April 2020 (12.9% [SE, 0.3]), in May 2020 (5.9% [SE, 0.2]), and over both months (9.3 [SE, 0.2]) (data are from eFig. 2B in Asch et al.[2]). Panel B shows the data from a hypothetical trial for an ineffective new agent used in May 2020 as compared with a control treatment used in April and May 2020. The data show that mortality was lower by 37% with the ineffective new agent than with the control treatment.

Spunti futuri

- Varianti
- Vaccini
- Nuovi trattamenti

Thank you for your attention