PREDICTORS OF FAILURE TO COVID-19 EARLY THERAPIES AND DRUGS EFFICACY COMPARISON BY EMULATION TRIAL

Valentina Mazzotta[1-2], Alessandro Cozzi Lepri[3], Cosmo Del Borgo[4], Silvia Rosati[1], Martina Rueca[5], Enrico Girardi[6], Loredana Sarmati[7], Claudio Mastroianni[8], Massimo Fantoni[9], Fabrizio Maggi[5], Emanuele Nicastri[1], Miriam Lichtner[4], Andrea Antinori[1], and the *Early Treatment for COVID-19 Lazio Study Group*

[1]Clinical Infectious Diseases Department, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; [2]PhD Course in Microbiology, Immunology, Infectious Diseases, and Transplants (MIMIT), University of Rome Tor Vergata, Rome, Italy; [3]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, London, UK;[4] Infectious Diseases Unit, Santa Maria Goretti Hospital, Sapienza University of Rome, Latina, Italy; [5]Laboratory of Virology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; [6] Scientific Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; [7]Infectious Diseases Unit, Tor Vergata University Hospital, Rome, Italy; [8]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy;[9]Infectious Diseases Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy;

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BACKGROUND

Although widespread vaccination and lower pathogenicity of the omicron variant had drastically reduced the rate of COVID-19-related hospitalization/death (CovH/D), real-world evidence can help to identify categories still at risk of severe outcomes and inform on the efficacy of different treatments used.

METHODS

Multicenter cohort of high-risk outpatients treated with monoclonal antibodies (mAbs) or antiviral drugs (AvD) for mild-to-moderate COVID-19 from March 2021 to May 2023 in the Latium Region.

The outcome was CovH/D by day 30 from baseline by fitting logistic regression models, including a specific set of potential confounders, for each exposure of interest: age>75 years; vaccination; calendar period (reflecting the main circulating VoC), immunocompromised status.

Among patients enrolled in 2022, the difference in risk between interventions (Sotrovimab=SOT; Molnupiravir=MLP; Remdesivr=RDV; tixagevimab/cilgavimab=T/C; nirmatrelvir/rit=N/r) was estimated in ***emulated parallel trials using a marginal structural model.***

*In this real-world study, the **incident risk of clinical failure** to early COVID-19 treatment was **3.08%** (95%CI 2.7-3.4). **Older, unvaccinated, and immunocompromised** patients had **the highest risk of severe COVID-19. Oral antivirals** showed **higher efficacy** in reducing disease progression compared to other drugs.*

RESULTS

12,466 patients enrolled [female 50.2%, median age 70 yrs (IQR 57-80), unvaccinated 21%, immunocompromised 23.2%] (Tab1).

The primary endpoint occurred in 384/12,466 pts, with a day-30 incident risk of 3.08% (95% CI:2.7-3.4%). After controlling for potential confounders, a higher risk was observed for older aged (OR 2.01; 1.64-2.46), unvaccinated (2.30;1.73-3.05), and immunocompromised (1.41; 1.09-1.82). Using the "Delta period" as a reference, a decreased risk was observed in the Omicron waves (Tab2).

Among the 10,042 patients treated in 2022 (1,919 SOT, 3,733 MLP, 1,447 RDV, 433 T/C, 2510 N/r), failure rate according to intervention varied from 0.87% (0.55-1.32) for N/r, 1.68% (1.2-2.1) for MLP, 3.0% (1.6-5) for T/C, 3.5% (2.7-4.5) for SOT and 5.1% (4.1-6.4) for RDV.

TAB.1 Population characteristics according to clinical outcome

Characteristics	CovH/D N= 384	Free of event N= 12082	p-value*	Total N= 12466
Gender, n(%)			0.014	
Female	169 (44.0%)	6090 (50.4%)		6259 (50.2%)
Age, years			<.001	
Median (IQR)	76 (62, 85)	69 (57, 79)		70 (57, 80)
Older than 75, n(%)	209 (54.4%)	4505 (37.3%)	<.001	4714 (37.8%)
Vaccination, n(%)			<.001	
None or incomplete[a]	148 (38.5%)	2460 (20.4%)		2608 (20.9%)
Full[b], not recent[c]	153 (39.8%)	6445 (53.3%)		6598 (52.9%)
Full[b], recent[d]	83 (21.6%)	3177 (26.3%)		3260 (26.2%)
Comorbidities, n(%)				
Cardio-metabolic (Obesity, diabetes, CVD[e])	221 (57.6%)	7664 (63.4%)	0.019	7885 (63.3%)
Hepatic Disease	15 (3.9%)	249 (2.1%)	0.013	264 (2.1%)
Cancer	38 (9.9%)	961 (8.0%)	0.168	999 (8.0%)
Immunocompromised status[f]	86 (22.4%)	2806 (23.2%)	0.705	2892 (23.2%)
Neurologic impairment	10 (2.6%)	231 (1.9%)	0.332	241 (1.9%)
Renal impairment	60 (15.6%)	1239 (10.3%)	<.001	1299 (10.4%)
COPD[g]	82 (21.4%)	2499 (20.7%)	0.750	2581 (20.7%)
Calendar period according to the main circulating VoC, n(%)			0.004	
March-May 2021 (B.1.1.7)	35 (11.8%)	265 (2.7%)		300 (2.9%)
June-December 2021 (B.1.617.2)	77 (20.5%)	1177 (9.8%)		1254 (10.1%)
January-March 2022 (BA.1)	110 (29.3%)	3487 (29.0%)		3597 (29.0%)
April-June 2022 (BA.2)	43 (11.5%)	2416 (20.1%)		2459 (19.8%)
July-December 2022 (BA.4/5)	92 (24.5%)	3916 (32.6%)		4008 (32.3%)
January- February 2023 (BQ.1)	12 (3.2%)	565 (4.7%)		577 (4.7%)
March-May (XBB)	6 (1.6%)	191 (1.6%)		197 (1.6%)
Viral sequence available, n(%)				
No	296 (77.1%)	9904 (82.0%)	0.014	10200 (81.8%)

*Chi2 and Mann-Whitney test

TAB.3 Unadjusted and adjusted marginal relative hazards of COVID-19-related hospitalisation or death by day 30

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Sotrovimab	1.00		1.00	
Molnupiravir	0.47 (0.33, 0.66)	<.001	0.43 (0.29, 0.65)	<.001

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Sotrovimab	1.00		1.00	
Nirmatrelvir/r	0.24 (0.15, 0.40)	<.001	0.32 (0.19, 0.55)	<.001

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Tixagevimab/cilgavimab	1.00		1.00	
Molnupiravir	0.56 (0.31, 1.01)	0.055	0.45 (0.22, 0.94)	0.033

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Tixagevimab/cilgavimab	1.00		1.00	
Nirmatrelvir/r	0.29 (0.15, 0.57)	<.001	0.29 (0.13, 0.63)	0.002

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Remdesivir	1.00		1.00	
Molnupinavir	0.32 (0.23, 0.45)	<.001	0.29 (0.20, 0.42)	<.001

	Unadjusted HR (95% CI)	p-value	Adjusted** HR (95% CI)	p-value
Remdesivir	1.00		1.00	
Sotrovimab	0.68 (0.49, 0.94)	0.021	0.77 (0.55, 1.09)	0.136

	Unadjusted HR (95% CI)	p-value	Adjusted** HR (95% CI)	p-value
Tixagevimab/cilgavimab	1.00		1.00	
Sotrovimab	1.19 (0.66, 2.15)	0.572	1.24 (0.67, 2.28)	0.498

	Unadjusted HR (95% CI)	p-value	Adjusted** HR (95% CI)	p-value
Molnupiravir	1.00		1.00	
Nirmatrelvir/r	0.52 (0.32, 0.84)	0.008	0.76 (0.45, 1.28)	0.299

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
Remdesivir	1.00		1.00	
Nirmatrelvir/r	0.17 (0.10, 0.27)	<.001	0.23 (0.14, 0.39)	<.001

*adjusted for age, immunosuppression, history of vaccination, duration of symptoms, hepatic and renal disease and censoring using IPW

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TAB.2 OR of COVID hospitalization or death

	Unadjusted OR (95% CI)	p-value	Adjusted1* OR (95% CI)	p-value	Adjusted2& OR (95% CI)	p-value
Age						
>75 vs. <=75	2.01 (1.64, 2.46)	<.001				
Vaccination						
None or incomplete	2.30 (1.75, 3.03)	<.001	2.46 (1.87, 3.24)	<.001	2.30 (1.73, 3.05)	<.001
Full, not recent[a]	0.91 (0.69, 1.19)	0.488	0.91 (0.69, 1.19)	0.496	1.01 (0.76, 1.34)	0.929
Full recent[b]	1		1		1	
Calendar period according to the main circulating VoC						
June-December 2021 (B.1.617.2)	1		1		1	
January-March 2022 (BA.1)	0.41 (0.31, 0.53)	<.001	0.37 (0.28, 0.49)	<.001	0.49 (0.37, 0.65)	<.001
April-June 2022 (BA.2)	0.23 (0.16, 0.33)	<.001	0.19 (0.13, 0.28)	<.001	0.26 (0.16, 0.41)	<.001
July-December 2022 (BA.4/5)	0.30 (0.23, 0.40)	<.001	0.25 (0.19, 0.34)	<.001	0.32 (0.17, 0.62)	<.001
January-February 2023 (BQ.1)	0.27 (0.15, 0.50)	<.001	0.22 (0.12, 0.40)	<.001	0.30 (0.13, 0.69)	0.005
March-May (XBB)	0.40 (0.18, 0.93)	0.034	0.36 (0.16, 0.83)	0.017	0.43 (0.16, 1.20)	0.107
Immunocompromised status						
Yes vs No	0.95 (0.75, 1.22)	0.705	1.21 (0.94, 1.56)	0.141	1.41 (1.09, 1.82)	0.008

*adjusted for gender and age

& separate adjustments for each exposure; a) Vaccination - for age, natural infection, immunodeficiency and calendar year; b) Calendar period according to the main circulating VoC - for previous natural infection and vaccination; c) Immunocompromised status - for age, vaccination and calendar year

Emulation trial for comparison of different treatment options showed higher efficacy of oral antivirals in the prevention of CovH/D compared to mAbs or RDV; no significant differences were observed between the oral antivirals or between mAbs and RDV, respectively (Tab3).

CONCLUSIONS

Despite the decreasing risk of CovH/D across the calendar periods, older aged, unvaccinated, and immunocompromised patients remained at the highest risk of developing severe COVID-19. Oral antivirals showed higher efficacy in reducing Cov/H, while no significant differences were observed between them or between mAbs and RDV. These data could help to tailor therapies according to different risk factors and specific contraindications.

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***Author Contact Information:* Valentina Mazzotta MD, e-mail: valentina.mazzotta@inmi.it**