ORIGINAL ARTICLES

Efficacy and safety of oral antivirals in individuals aged 80 years or older with mild-to-moderate COVID-19: preliminary report from an Italian Prescriber Center

Running title: Efficacy and safety of anti-COVID oral antivirals in the elderly

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SUMMARY

Introduction: Molnupiravir and Nirmatrelvir/ritonavir(r), have demonstrated to prevent the progression to severe COVID-19 in high-risk individuals. Real life data are lacking in the elderly.

Methods: All consecutive individuals aged ≥80 years with confirmed COVID-19 and mild-to-moderate illness who received an oral antiviral prescription between 11th January and 31st May 2022 were included in this retrospective single-centre study. The aim was to assess safety and effectiveness of oral antivirals in individuals ≥80 years with mild to moderate COVID-19.

Results: A total of 168 subjects ≥80 years were included. Molnupiravir was prescribed in 147 (87.5%) subjects whereas Nirmatrelvir/r in 21 (12.5%); 16 (9.5%) experienced at least one adverse event. Overall, 21 (12.5%) hospitalizations and five deaths were reported at 28 days. At multivariate analysis male sex (OR = 4.196, 95% CI = 1.479-11.908; p=0.007), a moderate illness at time of prescription (OR=10.946, 95% CI =2.857-41.395; p=0.0005) and a greater number of days from the onset of symptoms to the therapy (OR=2.066, 95% CI = 1.285-3.322; p=0.0027) were associated with hospitalization and/or death.

Conclusion: In this real-life setting, including older individuals' hospitalizations and mortality at 28 days remained low thanks to the prompt initiation of oral antiviral therapy. The use of oral antivirals can play a significant role in reducing healthcare costs and ensuring benefits among the elderly population.

INTRODUCTION

The Coronavirus Disease-19 (COVID-19) pandemic shows no signs of diminishing due to the constant spread of new variants characterized by high contagiousness and capable of evading the vaccines [1,2]. Noteworthy, older people are more likely to have a waning immune response despite a full vaccination compared to younger [3]. However, two oral antivirals, Molnupiravir and Nirmatrelvir/ritonavir(r), have recently revolutionized the early management of mild to moderate COVID-19 by blocking viral replication thus avoiding the inflammatory cascade that leads to

severe disease [4]. These two drugs can be prescribed within five days from the onset of symptoms in subjects who are not hospitalized for COVID-19, with no need for supplemental oxygen, and at higher risk of developing severe COVID-19. Although randomized trials have demonstrated safety and efficacy, real life data are still lacking, particularly among the elderly [5,6].

PATIENTS AND METHODS

All consecutive individuals aged ≥80 years with confirmed COVID-19 and mild-to-moderate illness who received an oral antiviral prescription between 11th January and 31st May 2022 in Taranto (Italy) and its Province were included in this retrospective single-centre study. The proposals of antiviral therapy were formulated and sent to our center by email from the general practitioners (GPs) or other specialists who identified high-risk subjects. Criteria inclusion were: 1) confirmed COVID-19; 2) onset of symptoms within five days; 3) at least one of the following comorbidities: obesity (body mass index ≥30); diabetes mellitus with organ damage or HBa1c >7.5%; chronic renal failure; chronic respiratory diseases; severe cardiovascular disease; immune deficiency; malignancies. Criteria exclusions were: 1) severe illness requiring oxygen support and/or hospitalization; 2) sever liver impairment 3) severe renal impairment (eGFR <30 mL/min/1.73m2). Mild to moderate illness was defined as reported in the COVID-19 Treatment Guidelines Panel. Mild illness included individuals who had any of the various signs and symptoms of COVID-19 (*e.g.*, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who did not have shortness of breath, dyspnoea, or abnormal chest imaging. Moderate illness included individuals who showed dyspnoea, evidence of lower respiratory disease during clinical assessment or imaging (where available) and who had an oxygen saturation (SpO2) ≥94% on room air at sea level.

Once eligibility for therapy was verified according to the current Italian Medicine Agency (AIFA) criteria, all patients or their caregivers were contacted by telephone to provide more information

regarding clinical conditions, vaccination status and daily therapies [7]. Therefore, antiviral therapy (Molnupiravir or Nirmatrelvir/r) was chosen after carefully evaluating drug-drug interactions by consulting a dedicated website [8]. Antivirals were administered respecting the recommended dosage [7]. The recommended dose of Molnupiravir is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. The recommended dosage of Nirmatrelvir/r is 300 mg: Nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) all taken together orally every 12 hours for 5 days. In subjects with moderate renal impairment, the dose of Nirmatrelvir/r was reduced to Nirmatrelvir/ritonavir 150 mg/100 mg every 12 hours for 5 days to avoid increased toxicity due to over-exposure (this dose adjustment has not been clinically tested).

Patients themselves or their caregivers following clinical signs of worsening (for instance: persistent fever, onset of breathlessness, reduced oxygen saturation etc) were asked to contact the GPs who activated the Special Units for Continuity of Care (USCA) or in severe cases, the Italian emergency telephone number, 118. Alternatively, our team was contacted directly and provided clinical suggestions.

A follow-up (FU) phone call was performed 28 days after the antiviral prescription to find out if any side effects in the course of therapy, all-causes hospitalizations or deaths had occurred.

The first end-point was to evaluate the efficacy of antivirals defined as rate of hospitalization and/or death at 28 days. The second end-point was to assess their safety in the course of treatment.

Statistics

Quantitative data were shown as means and standard deviation if normally distributed, as median and interquartile range (IQR) if assumption of normality was not acceptable. Shapiro-Wilk's statistics was used to test normality. Differences in continuous variables between groups were compared using Mann-Whitney U test. Categorical data were expressed as frequency and percentage. Chi-square test or Fischer's exact test was used to compare the groups. The possible association between the outcome and covariates such as age, sex, comorbidities, antiviral therapy,

COVID-19 vaccination, days after last vaccination, days from the onset of symptoms to prescription of antiviral therapy, were evaluated using a multivariable logistic regression model. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using the SAS/STAT® Statistics version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The study was approved by the Medical Ethics Committee of Brindisi, Italy (protocol code 0080398). The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. In any case, data were previously anonymized, according to the requirements set by Italian Data protection Code (leg. Decree 196/2003).

RESULTS

A total of 168 subjects were included: 122 (72.6%) constituted the group A (age 80-89) and 46 (27.4%) the group B (age ≥90). Demographic and clinical features of the two groups were similar (Table 1). Data regarding co-medications were complete and available for 75 patients. The main co-medications were oral anticoagulants (28/75, 37.3%) and statins (23/75, 30.7%).

Safety profile

Safety profile at 28 days are reported (Table 2). During the course of antiviral therapy, 16 (9.5%) experienced at least one adverse event without significant differences between the groups. Only one (0.6%) serious adverse event occurred, i.e. an extensive rash in an 80-year-old man leading to treatment discontinuation. Six supplementary discontinuations of therapy were observed: five due to voluntary suspension and one in an 80-year-old woman requiring hospitalization because of abdominal pain.

Clinical outcomes

A total of 21 (12.5%) hospitalizations were reported at 28 days; 9 out 21 were COVID-19 related with evidence of severe pneumonia causing acute respiratory failure, whereas the remaining twelve

were due as follows: two for congestive heart failure, one for abdominal pain, another for a stroke and eight for expiry of the general conditions including severe dehydration, senile cachexia and feeding difficulties. Overall, five deaths were observed: four due to COVID-19-related respiratory worsening and one because of senile cachexia. No deaths occurred among the subjects treated with nirmatrelvir/r.

Factors associated with hospitalization and/or death at 28 days

The association between the composite outcome (as hospitalisation and/or death at 28 days) and several covariates were assessed by performing a regression logistic analysis (Figure 1).

At multivariate analysis male sex (OR = 4.196, 95% CI = 1.479-11.908; p = 0.007), a moderate illness at time of antiviral prescription (OR = 10.946, 95% CI = 2.857-41.395; p = 0.0005) and a greater number of days between the symptoms onsetting and the therapy prescription (OR = 2.066, 95% CI = 1.285-3.322; p = 0.0027) remained independently associated with hospitalization and/or death at 28 days (Table 3 and Figure 2).

DISCUSSION

Currently molnupiravir and nirmatrelvir, represent a pivotal weapon in the early management of mild-to-moderate COVID-19 to prevent the progression to severe disease in high-risk subjects [4-6]. Their use has highlighted advantages on several aspects.

Firstly, they can easily be administrated at home, whereas monoclonal antibodies and remdesivir, given their parenteral administration, require a hospital setting thus resulting in higher costs and healthcare organizational issues.

Secondly, their antiviral activity against the omicron variant and subvariants spreading in the current scenario, is preserved, unlike some monoclonal antibodies that would seem to have lost their efficacy towards circulating variants [10, 11].

Moreover, COVID-19 is still fearful for the elderly characterized by poor immune response, inherent frailty and worse clinical outcomes compared to the younger [3,12-14].

We evaluated the safety and effectiveness of oral antivirals in older people with a high burden of co-morbidities. Randomized trials of molnupiravir and nirmatrelvir showed a lower incidence of hospitalizations and deaths than the placebo groups, 6.8% and 0.77%, respectively [5, 6]. However, these studies were performed mainly on young (median age 42 and 45 years, respectively) and unvaccinated subjects. Conversely, our study is focused on individuals aged 80 years or older, mostly vaccinated (95.2%) and having received a booster dose (91.6%) in the era of Omicron and subvariants. Only two subjects had received one dose. We did not find a significant impact of the number of doses in terms of hospitalization and/or death at 28 days. In fact, among the 21 subjects with the composite outcome, only one patient was unvaccinated, the remaining twenty had received the third dose.

In our study, the median time from the last vaccine dose to the onset of symptoms was 132 days (IQR 104-160). Considering a cut-off of 150 days from the last dose of vaccine, including the booster dose, no significant differences were observed in terms of clinical outcomes between individuals who received the last dose of vaccine for ≥150 days and those for <150 days. On one hand, this could be explained by considering that the Omicron variant, circulating from the beginning of 2022, was associated with lower rates of severe disease [15]. On the other side, we believe that early antiviral treatment might have contained the progression to severe illness regardless of vaccination status, despite this remains the principal measure in preventing severe COVID-19.

In addition, since the fourth dose, currently recommended in people over 60, had not been administered yet at the time of our study, its effects could not be assessed.

We encountered a higher rate of hospitalizations (12.5%) than those reported in the Move-Out study (7.3%) and the EPIC-HR trial (0.7%), but consistent with a recent real-life study that reported a progression of disease in 10.4% [16]. Conversely, in another study evaluating 145 patients treated

with molnupiravir, only 4 (2.7%) required hospital admission and no patients developed severe COVID-19, were admitted to the ICU, or died during the follow-up period [17].

Recently, a total of 2661 patients who received molnupiravir were propensity score-matched with 2661 patients who have not received molnupiravir (control group) [18]. A composite outcome occurred in 50 subjects (1.8%). Molnupiravir was not associated with a significant reduced risk of the composite outcome compared with the control group. However, subgroup analyses showed that Molnupiravir was associated with a significant decrease in the risk of the composite outcome in older patients, in females and in patients with inadequate COVID-19 vaccination.

In our study, male sex, moderate illness at the time of prescription and a longer time from the onset of symptoms to the therapy were associated with a higher likelihood of composite outcome. In this regard, the male versus female sex is a well-recognized risk factor for poor outcomes [19,20].

Although we could not perform a clinical examination as they mostly were outpatients, we can assume that the clinical information from the phone call could correspond to a precise clinical pattern (mild vs moderate illness).

Since oral antivirals are effective in the early phase of infection, we found that subjects who started therapy later were more likely to have worse outcomes. Possible reasons for prolonged initiation of treatment included: delay in communicating symptoms and consequently in confirming the diagnosis as well as lack of knowledge and confidence of these therapeutic options among the patients.

Overall, oral antivirals were well tolerated. Compared to those reported in the randomized trials (30.4% in the Move-Out study and 22.6% in the EPIC-HR trial), the incidence of adverse events was lower (9.5%) but similar (6.8%) to that observed in the study of De Vito et al. [16].

Moreover, we are aware of the possibility of a partial underestimation of self-reported side effects incidence due to the poor perception of the same by age-old subjects or their caregivers.

Our study has several limitations. Primarily, this is a single-center retrospective observational study. In the second place, antiviral treatment groups could not be compared. In fact, only 21 patients were

197 treated with Nirmatrelvir/r since this drug is difficult to manage given the relevant drug-drug
198 interactions, particularly in elderly patients taking numerous co-medications whose concomitant use
199 is not recommended. Molnupiravir has a good profile of drug-drug interactions and do not require
200 dose adjustments based on renal filtrate compared with Nirmatrelvir/r. In the elderly, the renal
201 filtrate is frequently impaired and tends to further reduce due to the infectious state and dehydration,
202 thus leading to accumulation of drugs and toxicity.
203 Moreover, in January 2022 and, partially, February 2022, molnupiravir only could be prescribed as
204 the use of Nirmatrelvir had not been allowed in Italy yet. Third, the choice of antiviral, even if
205 based on the good clinical practice and after assessing clinical history and drug-drug interactions,
206 reflected the experience of a single equipe. Lastly, data on the biochemical parameters and
207 radiological features were lacking in the majority of cases.
208 Nevertheless, this report provides several insights from clinical practice and reinforces the utility of
209 early antiviral treatment in a setting of older people at high-risk.
210 In this real-life study, including older individuals' hospitalizations and mortality at 28 days
211 remained low thanks to the prompt initiation of oral antiviral therapy. Therefore, making efforts to
212 provide earlier access to care becomes essential.
213 Finally, the use of oral antivirals can play a significant role in reducing healthcare costs and
214 ensuring benefits among the elderly population.
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219

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CONFLICT OF INTEREST

The authors declare they have no financial interests that are directly or indirectly related to the work submitted for publication.

AUTHOR CONTRIBUTIONS

Data analysis: GB, MG, NB. Paper writing: GB, MG, GbB. Study design: GB, GbB. Data collection and record: GB, SP, GD.

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Table 1 - Clinical characteristics of the 168 patients.

	Total	Group A 80-89 yrs	Group B ≥90 yrs	p
No.	168	122	46	
Age, mean (range)	86.5 (82.5-90)	84 (82-87)	93 (91-96)	
Sex				
Female	102 (60.71%)	68 (55.74)	34 (73.91)	0.03
Comorbidities				
Cardiovascular diseases	105 (62.28)	75 (61.98)	30 (63.04)	1
Diabetes mellitus	20 (11.98)	14 (11.57)	6 (13.04)	0.79
Obesity	26 (15.57)	20 (16.53)	6 (13.04)	0.64
Malignancies	23 (13.77)	18 (14.88)	5 (10.87)	0.62
Respiratory diseases	40 (23.95)	27 (22.31)	13 (28.26)	0.42
Chronic renal failure, eGFR ≥ 30 ml/min	26 (15.57)	18 (14.88)	8 (17.39)	0.81
Immunodeficiency primary or secondary	9 (5.39)	0	9 (7.44)	0.06
Nervous system diseases	18 (10.71)	12 (9.84)	6 (13.04)	0.58
Two or more comorbidities	74 (44.05)	54 (44.26)	20 (43.48)	0.13
Moderate illness	14 (8.3)	10 (8.2)	4 (8.7)	0.91
Days from onset of symptoms to antiviral prescription	2.5 (2-3)	3 (2-3)	2 (2-3)	0.24
Use of Molnupiravir	147 (87.50)	106 (86.89)	41 (89.13)	0.82
Use of Nirmatrelvir/ritonavir	21 (12.50)	16 (13.11)	5 (10.87)	0.82
Guests of long-term facilities	23 (13.77)	13 (10.74)	10 (21.74)	0.08
Patients already hospitalized not for COVID-19	17 (10.24)	14 (11.67)	3 (6.52)	0.4
At least one dose of anti-SARS-CoV2 vaccine	160 (95.24)	116 (95.08)	44 (95.65)	1
Patients who underwent booster to anti-SARS-CoV2 vaccine	154 (91.67)	111 (90.98)	43 (93.48)	0.76
Time (days) from last dose of vaccine to positive swab	132(104-160)	130.5 (104-157)	147.5 (111.5-162)	0.34

297 **Table 2 -** Safety profile and clinical outcomes according to age-groups and antiviral therapy.

	Total	**Molnupiravir**			**Nirmatrelvir/r**		
		N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Groups		**A**	**B**	**Tot**	**A**	**B**	**Tot**
Age, yrs		**80-89**	**≥ 90**		**80-89**	**≥ 90**	
N.	168	106	41	147	16	5	21
Side effects	16 (9.5)	11 (10.3)	1 (2.4)	12 (8.1)	3 (18.7)	1 (20)	4 (19)
Headache	1 (0.59)	1 (0.9)	0	1 (0.68)	0	0	0
Diarrhoea	5 (2.9)	4 (3.7)	0	4 (2.7)	1 (6.2)	0	1 (4.7)
Abdominal pain	2 (1.2)	1 (0.9)	0	1 (0.68)	1 (6.2)	0	1 (4.7)
Fatigue	1 (0.59)	0	1 (2.4)	1 (0.68)	0	0	0
Nausea	4 (2.3)	2 (1.8)	0	2 (1.3)	1 (6.2)	1 (20)	2 (9.5)
Rash	2 (1.2)	2 (1.8)	0	2 (1.3)	0	0	0
Itching	1 (0.59)	1 (0.9)	0	1 (0.68)	0	0	0
Serious adverse events	1 (0.59)	1 (0.9)	0	1 (0.68)	0	0	0
Discontinuation of therapy	7 (4.1)	3 (2.8)	2	5 (3.4)	2 (12.5)	0	2 (9.5)
Hospitalizations	21 (12.5)	11 (10.3)	6 (14.6)	17 (11.5)	3 (18.7)	1 (20)	4 (19)
Hospitalization COVID-19-related	9 (5.3)	4 (3.7)	2 (1.2)	6 (4)	3 (18.7)	0	3 (14.2)
Hospitalization not COVID-19-related	12 (7.2)	7 (6.6)	4 (9.7)	11 (7.4)	0	1 (20)	1 (4.7)
Deaths	5 (2.9)	4 (3.7)	1 (2.4)	5 (3.4)	0	0	0
COVID-19-associated	4 (2.3)	3 (2.8)	1 (2.4)	4 (2.7)	0	0	0
Not COVID-19-associated	1 (0.59)	1 (0.9)	0	1 (0.68)	0	0	0

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Table 3 - Univariate and multivariate analysis to evaluate factors associated with hospitalizations and/or death at 28 days.

Parameter	*Univariate model*			*Multivariate model*		
	OR[1]	**IC95%**	**p-value**	**OR[1]**	**IC95%**	**p-value**
Sex [male vs female]	3.654	1.388-9.621	0.0009	4.196	1.479-11.908	0.007
Age [≥90 vs 80-89]	1.385	0.521-3.684	0.3326			
Cardiovascular diseases [Yes vs No]	0.783	0.31-1.978	0.6044			
Respiratory diseases [Yes vs No]	0.719	0.227-2.276	0.5749			
Immunodeficiency primary or secondary [Yes vs No]	2.09	0.404-10.8	0.3791			
Diabetes mellitus [Yes vs No]	0.749	0.161-3.486	0.7123			
Obesity [Yes vs No]	0.242	0.031-1.887	0.1758			
Chronic renal failure [Yes vs No]	1.326	0.408-4.316	0.6389			
Malignant tumours [Yes vs No]	2.222	0.726-6.803	0.1619			
Nervous system diseases [Yes vs No]	1.467	0.386-5.567	0.5736			
Two or more comorbidities [Yes vs No]	0.755	0.295-1.931	0.5579			
Guests of long-term facilities [Yes vs No]	0.122	0.007-2,217	0.1552			
Antiviral therapy [Molnupiravir vs Nirmatrelvir/r]	0.556	0.167-1,847	0.3377			
At least one dose of anti-SARS-CoV2 vaccine [Yes vs No]	1	0.117-8.559	1			
Booster of anti-SARS-CoV2 vaccine [Yes vs No]	1.94	0.241-15.648	0.5337			
Day after last vaccination [+1 day]	1.002	0.994-1.011	0.5561			
Last vaccination more of 150 days [Yes vs No]	1.054	0.395-2.816	0.9157			
Severity of symptoms [Moderate vs Mild illness]	10	3.064-32.64	0.0001	10.946	2.857-41.395	0.0005
Days from onset of symptoms to antiviral prescription [+1 day]	1.98	1.271-3.085	0.0025	2.066	1.285-3.322	0.0027

[1]adjusted by Wald methods; IC: Confidence interval; OR: Odds ratio

Figure 1 - Forest plot of odds ratio and their 95%CI calculated by a univariate logistic regression model.

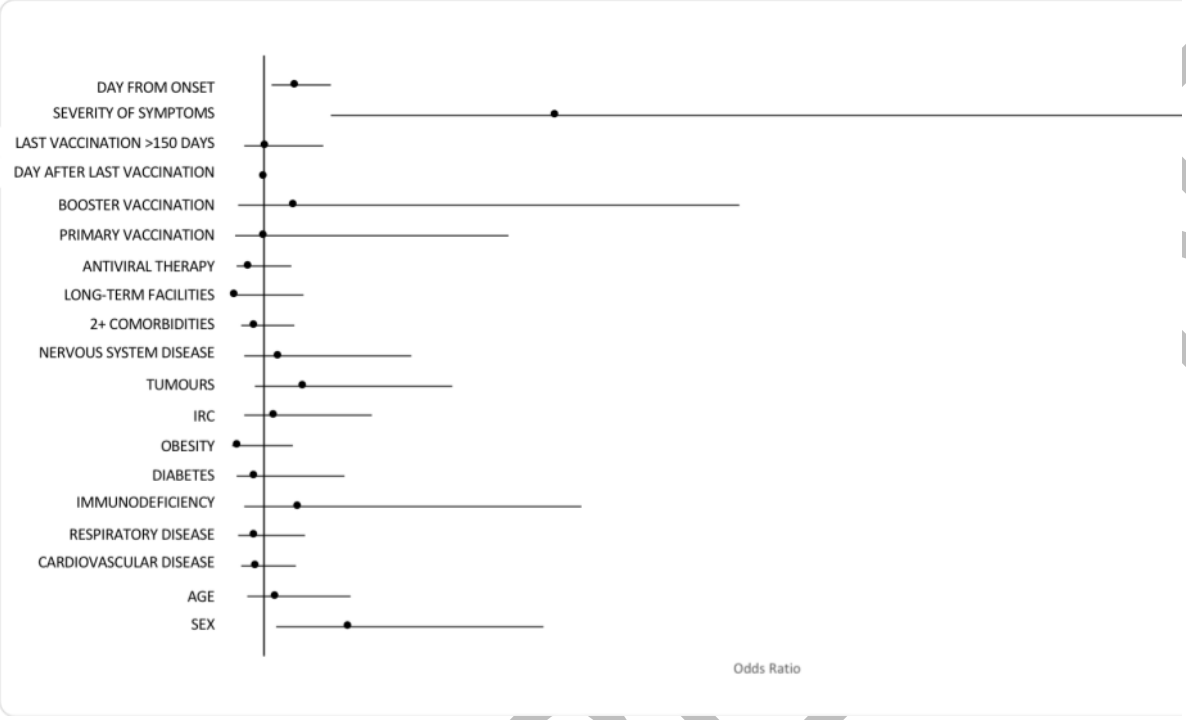
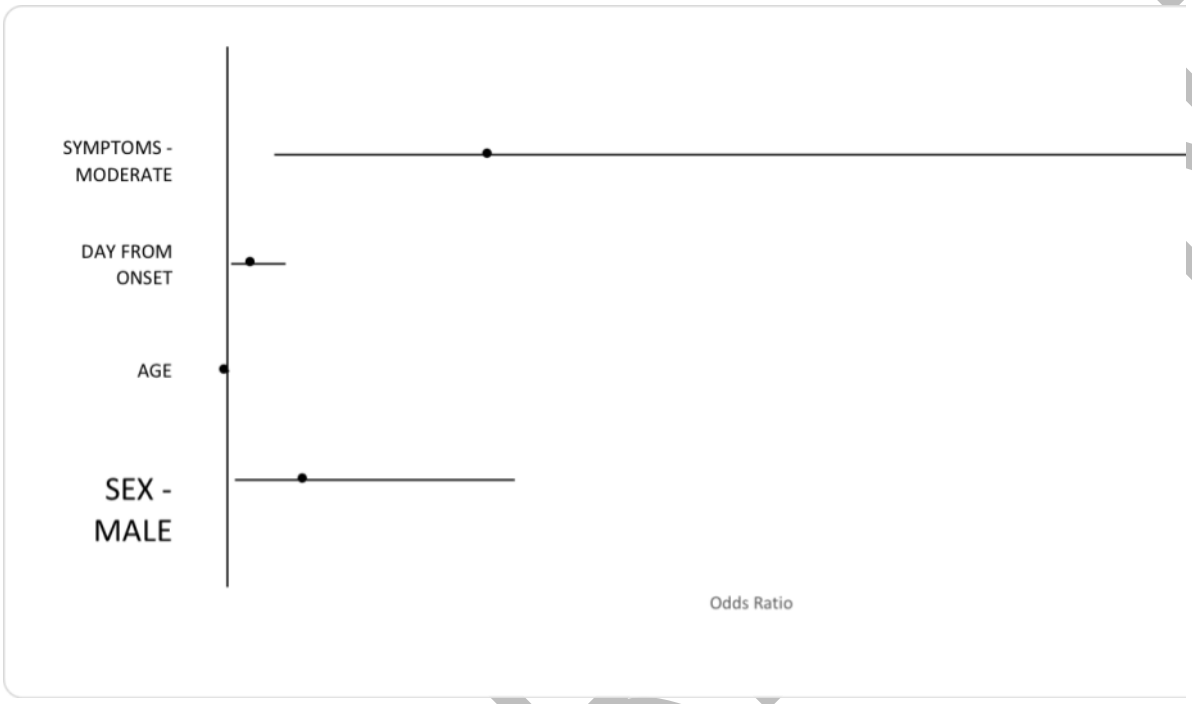


Figure 2 - Forest plot of odds ratio and their 95%CI calculated by a multivariable logistic regression model.



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