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*Coronavirus Pandemic*

# Efficacy of Linezolid in the management of pneumonic COVID-19 patients. Bioinformatics-based clinical study

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## Abstract

Introduction: At the beginning in July 2023, there has been a significant increase in daily hospital admissions attributed to the new variant of COVID-19. Aim of this study is to explore the clinical benefits and outcomes of using linezolid in the management of pneumonic COVID-19 patients.

Methodology: The study included 230 patients with SARS-CoV-2 infection confirmed by RT-PCR. Group 1: 118 patients were managed with Linazolid alongside steroids. Group 2: (control group) patients treated according to the Protocol for Egyptian COVID-19 management outlines and WHO guidelines (112 patients). Each patient group was categorized into 3 age groups: 20-40 years, 41-65 years, and over 65 years. Patients were carefully followed up until recovery or mortality. A docking analysis was carried out to investigate the potential of linezolid to act as an $M^{pro}$ inhibitor.

Results: Group 1's average recovery time was 15.1 days in contrast to 18.7 days for Group 2 (control). There were no deaths reported. In silico investigations revealed that Linezolid was able to achieve a binding mode comparable to that of the co-crystalized inhibitor.

Conclusions: Linazolid is considered an effective antiviral weapon against SARS-COV-2. It could be used in the management plan of pneumonic individuals due to SARS-COV-2 infection. We recommend using it to combat the current wave caused by Omicron EG-5 Variant.

**Key words:** Linazolid; pneumonia, SARS CoV-2; bioinformatics.

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## Introduction

World Health Organization declares that COVID-19 is no longer a "global health emergency," while it is noted that it still poses a serious global health danger [1,2].

Following an examination of the decreasing trend in COVID-19 deaths, the decrease in hospital admissions and intensive care cases associated with the virus, and the substantial levels of population immunity to SARS-CoV-2, the World Health Organization (WHO) emergency committee concluded that COVID-19's status should be changed to that of a persistent and ongoing health issue. This means it is no longer categorized as a global health disaster of worldwide importance [2].

However, beginning in July 2023, there has been a significant increase in daily hospital admissions connected to COVID-19. By August 4th, these admissions had more than doubled over the previous four weeks. Furthermore, the number of patients hospitalized largely as a result of COVID-19 has more than doubled throughout this period. Given these events, it is reasonable to conclude that a new COVID-19 wave has begun [3].

Recent testing has revealed that a unique strain of the pandemic coronavirus is spreading across the globe. This novel variation, dubbed "eris" is distinguished by major spike alterations that improve its ability to elude the immune response. According to the World Health Organization's most recent risk assessment, the omicron EG.5 variation has a higher prevalence and a faster rate of expansion [4].

However, there is currently no definite pharmacological remedy that has been demonstrated to result in true and significant improvement in the morbidity of individuals infected by COVID-19. Until now, certain therapeutic agents have shown effectiveness against SARS-CoV-2 in laboratory conditions or potential for treatment in non-randomized trials [5].

Until now, the Coronavirus Disease 2019 (COVID-19) Treatment Guidelines have been continuously revised to keep up with the rapid pace and rising volume of knowledge about COVID-19 treatment. Very recent updates were issued in July 2023 [6].

Antibiotics were one of the most common types of medications used to combat COVID-19. The amalgamation of drug manufacturing, Bioinformatic, and electronic structure methodologies can help in the search for effective treatments and medication regimes for SARS-CoV-2 [7-9].

The World Health Organization (WHO) has advised that antibiotics be used in managing individuals infected with SARS-CoV-2 patients. Simultaneously, advice was offered emphasizing the significance of a complete antibiotic administration strategy. This included taking the conservative approach of not prescribing antibiotics to people with mild to moderate COVID-19 until there was convincing proof of a bacterial infection [10,11].

As a result, the fundamental purpose of this research is to highlight the therapeutic benefits and outcomes of utilizing Linezolid in the care of COVID-19 patients, as well as to elucidate the role of bioinformatics in evaluating the possible interaction between Linezolid and the SARS-CoV-2 major protease enzyme.

## Methodology

*Study Design*

Hospital-based study involving 230 (107 male) COVID-19-infected patients confirmed by reverse transcription-polymerase chain reaction (RT-PCR) was carried out. All participants complied with the requirements for inclusion. As per the Helsinki Declaration, the study protocol was approved by the Beni-Suef University Faculty of Medicine's Research Ethical Committee (REC-FMBSU-12022023/Eid). Participants endorsed written statements of informed consent. The clinical study was conducted in the hospital's isolation unit from 15 January to 20 April 2022.

*Procedure*

The study focused solely on moderate and severe cases, with diagnoses made according to the criteria established by the World Health Organization (WHO) (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1). Linezolid was administered to the patients, with steroids added to the management plan. The intravenous dose of Linezolid was 600 mg every twelve hours for ten days. Dexamethasone 8 mg was the steroidal drug used. The patients were divided into two categories: Group 1 comprised patients treated with Linezolid (118 patients), while Group 2 (the control arm) included patients treated according to the WHO guidelines (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1) and the Egyptian protocol for managing COVID-19 which did not include Linezolid (112 patients).

The patients were monitored daily until their disease symptoms improved and their COVID-19 PCR tests came back negative. A follow-up was also performed to estimate the total period of steroid usage, as well as the recovery time. The length of recovery is calculated by counting the days between a positive confirmed COVID-19 PCR and a negative confirmed COVID-19 PCR. To assess the impact of age on the duration of disease recovery, each group was categorized into three age brackets: 20-40, 41-65, and above 65 years

*Inclusion Criteria*

- Patients over the age of 18 years
- Results indicate a positive infection for the COVID-19 using RT-PCR.
- Cases ranging from mild to severe with typical symptoms.
- Patients who are not receiving any other antiviral medications.

*Exclusion criteria*

- Patients suffering from decompensated hepatic cirrhosis.
- Patients who are pregnant or lactating.
- Patients under the age of 18.

*Molecular Docking*

The Protein Data Bank was used to import the crystal structure of the COVID-19 primary protease in association with an inhibitor (www.rcsb.org). The imported molecule was COVID-19 main protease in complex with the chemical compound with the formula N-[(5-methylisoxazol-3-yl)carbonyl] alanyl-L-valyl-N~1~-((1R,2Z)-4-(benzyloxy)-4-oxo-1-{[(3R)-2-oxopyrrolidin-3-yl].methyl}but-2-enyl)-L-leucinamide, which corresponds to the Protein Data Bank identification code 6LU7.

The three-dimensional (3D, Mol2) Linezolid molecule was utilized in the molecular docking assay using Molegro Virtual Docker 6. To ensure efficient protein-ligand binding, the co-crystallized ligand and the interfering crystallographic water molecules were taken out of the structure [12,13]. Molecular docking calculations for Linezolid and COVID-19 main protease inhibitor with that enzyme were estimated using Molegro Virtual Docker 6, with a spherical region with a radius sufficiently large to accommodate the cavity located at the active site of the protein of interest, enabling the ligand to explore and interact. Based on their energy scores, various ligand poses were searched and ranked.

Stronger ligand-protein interactions and binding affinities are indicated by MolDock scores that are lower [14]. For the best poses of the ligands with the lowest Moldock Scores, Molegro Data Modeller was used to compute the binding affinities in the current study. To verify the accuracy and validity of Molegro Virtual Docker 6 software, the root mean square deviation (RMSD) value of the redocking process of the co-crystallised inhibitor returned into the binding pocket of the target protein was estimated.

## Results

*Clinical outcomes*

In this study, 107 males and 123 females were followed from January to April 2022 in Egypt. The oldest and youngest patients were 80 and 18, respectively. The mean length of days of steroid consumption in Group 1 ± standard error was 5 ± 0.5 days and for Group 2 (control) was 7.7 ± 0.3 days. Furthermore, the mean recovery time for Group 1 ± standard error was 15.1 ± 0.86 days, and for Group 2 (control) was 18.7 ± 0.6 days.

At the finale of the study, all the patients had improved, and assisted ventilation was not required.

The recovery time for Group 1 was 10.8, 13.5, and 17 days for the age categories 18-35, 36-55, and more than 55 years, respectively. The recovery time for Group 2 (control) was 15, 16, and 20 days for the age categories 20-40, 41-65, and more than 65 years, respectively.

According to previous research, using Linezolid combined with steroids to treat individuals with pneumonic COVID-19 individuals either severe or moderate stage caused recovery times comparable to those produced from treatment with standard-of-care medications (i.e., a positive control).

As a result, our suggested simplified management plan, which includes only two drugs (dexamethasone + Linezolid), will benefit patients better than the current protocol, which includes multiple drug categories with different interactions. Patients who received such commonly used multi-drug treatment protocols experienced more side effects; therefore, the current study's simple treatment protocol, which produced comparable results, will be preferable, especially for elderly patients.

*Docking results*

The molecular docking strategy identifies and investigates the crucial interactions between amino acids in protein molecules and ligands that have low-energy models [15]. The redocking simulation of the co-crystalized protein with its inhibitor revealed a mean square standard deviation (RMSD) value of 0.48, which indicates reliable docking [16]. Figure 1 displays the co-crystalized inhibitor that overlaps with the produced pose during the redocking process.

Linezolid molecule was investigated for potential binding into the protein active site using the Molegro docking algorithm. Linezolid compound has been docked targeting the major protease enzyme of COVID-19 (Figure 2). The molecular docking assay revealed that Linezolid is a promising inhibitor with a

**Figure 1.** Overlapping of co-crystalized inhibitor N3 with the produced pose during the re-docking process.

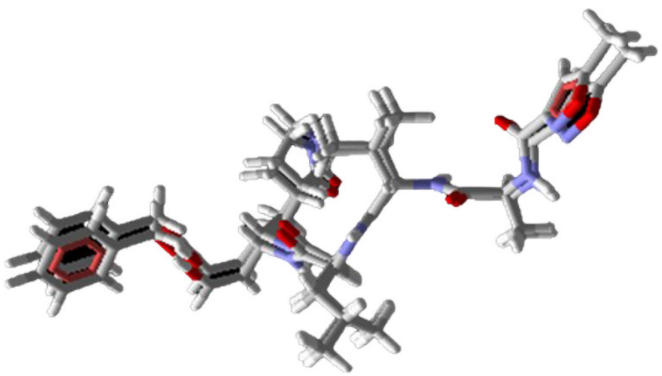


**Figure 2.** Molecular surface view and ribbon diagram display docked confirmations of Linezolid compound into the binding site of COVID-19 main protease enzyme.

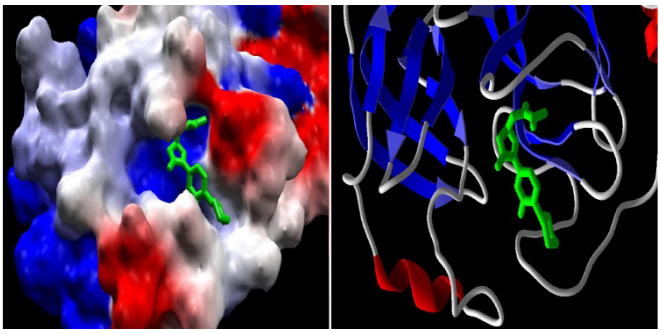
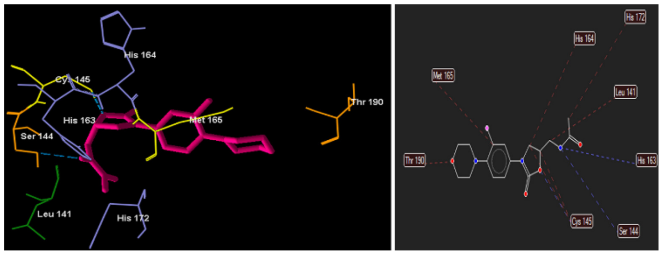


**Figure 3.** 3D and 2D intermolecular residual interactions maps of Linezolid against the active pocket of the COVID-19 main protease enzyme, where the blue dotted lines represent the hydrogen bonds, while the red dotted lines represent the steric interactions.




lower binding affinity score of -28.35 compared to the N3 enzyme inhibitor with a binding affinity of -18.79.

Linezolid is a good fit for the active binding pocket of the COVID-19 primary protease enzyme and has 3 hydrogen bond interactions with amino acids Ser144, Cys145, and His163 at the active site as displayed in Figure 3.

As shown in Table 1, the mutual amino acid residues with re-docked enzyme inhibitor, Linezolid, and co-crystalized ligand in their molecular interactions with COVID-19 main protease are Cys145, His164, and Thr190.

## Discussion

According to the findings of this study, linezolid has potential antiviral properties besides antibacterial properties. Linezolid is the first antibiotic in the class of oxazolidinones. By attaching to the 50S ribosomal subunit, it suppresses protein synthesis in the bacterial cell. It is approved to treat serious infections caused by several resistant mutant strains of methicillin-resistant strains (MRSA), as well as vancomycin-resistant strains (VRE) in addition to several Gram-negative and Gram-positive bacterial strains [17] Linezolid is recommended to treat pneumonia caused by MRSA [18,19].

In this study, we looked at the efficacy of short-term dexamethasone treatment combined with Linezolid in pneumonic COVID-19-infected individuals with either severe or moderate clinical manifestations, hypothesizing that the antibacterials could also have an extra beneficial antiviral inhibitory property in addition to protecting against superinfections and/or co-infections. In general, the duration of steroid therapy for Covid-19 patients ranges from 3-12 days [20-22].

The patients who used Linezolid required an average of 5 to 6 days of steroid therapy, according to our findings. This demonstrates Linezolid's satisfactory success in treating COVID-19 patients, with improvement in the clinical symptoms beginning on the fifth or sixth day after initiation.

Additionally, it was found that when Linezolid was given two times per day for ten days at a dose of 600 mg, it reduced the length of the patients irritating symptoms and time for clinical improvement among patients with pneumonic involvement either severe or moderate degrees, with minimal side effects. As a result, this dosing regimen has the potential to reduce COVID-19 morbidity and mortality.

A recent cohort highlighted that linezolid exhibited effectiveness as a treatment option for bacterial nosocomial pneumonia in patients with COVID-19 [23]. Another study found that linezolid has superior clinical and microbiological efficiency than vancomycin, a famous and common antibacterial weapon prescribed by different specialties among different physicians [24]. Linezolid is superior to vancomycin because it penetrates more into respiratory secretions. Spinoni *et al.* also used linezolid in treating a COVID-19 patient who had previously received

**Table 1.** Molecular docking assay of COVID-19 main protease.

| Enzyme | *ligand* | *Binding Affinity* | *HB interacting residues* | *H-bonds and steric interacting residues* |
|---|---|---|---|---|
| COVID 19 main protease | Redockd inhibitor N3 | -18.79 | Thr26, Ser46, Cys145, Gln189, and Thr190 | Thr25, Thr26, Ser46, Met49, Asn142, Gly143, Cys145, His164, Glu166, Gln189, and Thr190 |
| | Linezolid | -28.34 | Ser144, Cys145, and His163 | Leu141, Ser144, Cys145, His163, His164, Met165, His172, and Thr190 |
| | Co-crystalized binder N3 | | Phe140, Gly143, His164, Glu166, Gln189, and Thr190 | Thr26, Phe140, Gly143, Cys145, His163, His164, Glu166, Gln189, and Thr190 |

ticoplanin and ceftazidime/avibactam treatment. The ticoplanin was then replaced with linezolid [25]. The effectiveness of linezolid in treating pneumonia in COVID-19 patients for improving the clinical status of and decreasing the mortality caused by coinfections was reported by a previous study [26]. In addition to the antibacterial effect, a previous study reported that Linezolid shows promise as a potential medication for impeding SARS-CoV-2 infection [27].

The previously stated mean total length of COVID-19 clinical symptoms of moderately cured patients was 11.5 ± 5.7 days. Significant irritating patient complaints vary depending on both sex and age category [28].

In our research, individuals received COVID-19 medications until full recovery (recovery time) for an average of 10-17 days, depending on age, indicating that Linezolid is effective in the management of individuals with pneumonia arising due to COVID-19 infection.

The group category (over 65 years) had a longer time for improvement than the younger patients aged 40-65 years, while this latter category (40-65 years) had a slower recovery period than the youngest patients in our cohort 20- 40 years. This indicates that the older the age the slower the improvement. The younger age category is less likely to develop critical or severe disease stages and recover from COVID-19 symptoms faster than individuals of older ages. This has also been demonstrated in other studies by Salah *et al.* [29].

Our results revealed that using Linezolid in combination with steroidal therapy for the treatment plan of pneumonia cases either of the severe or moderate degrees of COVID-19 infection caused recovery periods similar to the standard of care therapies (i.e., positive control). Therefore, our suggested simplified management plan, which includes only two pharmaceutical drugs (dexamethasone + Linezolid), will be more beneficial to patients than the current complex regimen, which includes several therapeutic agents. When patients were subjected to the current procedure involving multi-drug therapy, they experienced a higher occurrence of several side effects, so the proposed simple treatment regimen with favorable outcomes will be preferred, especially for geriatric individuals.

Our current study's main strengths are as follows: (i) the study's relatively large sample size (230 patients); (ii) the first clinical research to show the efficiency of Linezolid in the management of pneumonic patients due to SARS COV-2 infection, either moderate or severe stage.

The main limitations of the current study: (i) hospital-based experience and not a multicenter study; (ii) it provided no definite conclusion about the antibiotic's efficacy in the patient's own body; (iii) monitoring the viral load in the treated group was not done so, we could not draw more thorough recommendations about the effectiveness of the antibacterial agent to eliminate viral disease.

## Conclusions

Drug repurposing has the potential to reduce the cost and time associated with designing new drugs. Linezolid has potent antiviral properties and is effective against a variety of viruses, including MERS and SARS. Dual therapy with Linezolid and steroids is thought to be superior to using either antibiotics or steroids alone. The duration of clinical improvement increased with age. Compared to older patients, younger individuals are generally less prone to developing severe COVID-19 cases and tend to recuperate from symptoms more rapidly.

Based on our conclusions that Linezolid provides extra benefits to SARS-COV-2 pneumonic patients due to its potential antiviral properties Furthermore, their remarkable antibacterial properties contribute to their effectiveness, our main recommendation is to combine this drug alongside dexamethasone in the treatment of COVID-19 pneumonic cases in the current wave caused by Omicron EG-5, which had started in several countries in august 2023.

### Authors' Contributions

Dr. Ragaey Ahmad Eid acts as the principal investigator for the study, with all authors actively contributing to the study's design, implementation, analysis, and interpretation of the results. Additionally, they collectively collaborated in writing the manuscript, and all authors provided their final approval before submission.

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