

## Article

# Pharmacological Profiles and Recovery Predictors in Severe COVID-19

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## Abstract

This study analyses the pharmacological profiles of medications administered to critically ill COVID-19 patients to evaluate their efficacy regarding recovery rates and duration of hospitalization. The results demonstrate a significant difference in clinical outcomes. While the administration of Ceftazidime, Ceftriaxone, and Oseltamivir was associated with negative survival trends, Dexamethasone and Favipiravir were associated with a fourfold higher probability of survival in severe cases. Notably, no pharmacological intervention significantly reduced the length of hospital stay; instead, recovery duration was primarily influenced by comorbidities such as obesity, cardiovascular disease, and diabetes. Furthermore, age and preexisting physiological conditions remained primary predictors of mortality. Observational analysis in our study for drug repurposing identified Amikacin, Remdesivir, and Rivaroxaban as potential therapeutic candidates. However, Dexamethasone was identified as the most effective treatment for recovery, likely due to a molecular structure with high potential binding affinity to the SARS-CoV-2 virus. These findings suggest that while specific repurposed drugs offer measurable benefits, patient history remains a critical determinant of outcomes, highlighting the necessity for further research to refine therapies against emerging viral pathogens.



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## 1. Introduction

The emergence and success of infectious diseases are driven by a dynamic interplay between three key factors: the microbe, the host, and the environment. Disease incidence depends on the host's ability to withstand the burden of infectious agents, as well as the quantity and virulence of those microbes. Furthermore, a closed-system environment increases host exposure to these agents, heightening the risk of infection. For antimicrobials

to be effective, they must target at least one specific mechanism of action within the microbial life cycle.

In the case of SARS-CoV-2, the infection process begins when the spike (S) glycoprotein on the viral surface binds to the angiotensin-converting enzyme-2 (ACE-2) receptor on the host cell. The virus is composed of four primary structural proteins—spike (S), membrane (M), envelope (E), and nucleocapsid (N)—which facilitate viral entry, assembly, and release [1]. Additionally, sixteen non-structural proteins (NSPs) assist in immune escape [2]. This evasion occurs by suppressing interferon production and preventing the formation of phagolysosomes, which impairs the innate immune response across various cells and pathways, including macrophages, dendritic cells, T cells, NK cells, and the NLRP3 inflammasome [3].

Repurposed drugs for COVID-19 patients aim to either inhibit viral replication or manage an overwhelmed immune response, often characterized by elevated circulatory cytokines such as IL-2 and IL-6 [4]. Despite their theoretical mechanisms, several promising drugs have not proven effective in practice. These interventions include: (1) interfering with replication: ACE-2 glycosylation (hydroxychloroquine [5,6], ivermectin [7]), phagocytosis (hydroxychloroquine [5,6], azithromycin [8]), neuraminidase inhibition (oseltamivir [9]), and blocking importins (ivermectin [7]); and (2) modulating immune response: inhibiting cytokine release (hydroxychloroquine [10]) or cytokine production (azithromycin [8], ivermectin [7]).

Research indicates that antibiotics are not associated with higher survival rates, as their use is similar between survivors and non-survivors [11]. While some antivirals improve clinical outcomes, they have not been significantly linked to reduced mortality [12]. Specifically, previous studies found that favipiravir improved patient outcomes, whereas azithromycin and oseltamivir did not [13].

The presence of the virus within host cells triggers an inflammatory cascade that can become severe and life-threatening. Because viral loads and interleukin levels serve as critical predictor markers in severe cases, many drugs continue to be repurposed for treatment. This study aims to evaluate the rationality of using these various drugs for patients facing critical COVID-19 illness.

## 2. Results

Sixty-two patients among 244 severe to critical COVID-19 patients were  $\geq 65$  years old. More than fifty percent (124/244) were critically ill COVID-19 patients (Supplementary Table S1). Besides respiratory disease, there were eleven comorbidity categories, with blood-related disorders and diabetes being the two most prevalent.

### 2.1. Drug Use Profile

#### 2.1.1. Antiinfectives and Antimycotics

Levofloxacin or moxifloxacin was the most used antibiotic in hospitals A, B, D, and E; whereas azithromycin was most used in hospital C (Table 1a). The number of azithromycin uses in RS C was 39.8 DDD per 100 bed-days. This number implies that 39.8 out of 100 patients a day use 1 DDD azithromycin (0.3 g orally or 0.5 g parenterally).

**Table 1.** (a) DDD per 100 bed-days antiinfectives (J01) and antimycotics for systemic use (J02); (b) DDD per 100 bed-days antivirals (J05); (c) DDD per 100 bed-days anti-inflammatory nonsteroids (M01A).

(a)												
Group	Name	ATC Code	Hospital A		Hospital B		Hospital C		Hospital D		Hospital E	
			DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days
Antiinfectives for systemic use (J01)												
Access (1)												
Penicillin beta-lactam (J01C)	Ampicillin	J01CA01	0	0	0	0	1	0.3	0	0	0	0
	Ampicillin and sulbactam	J01CR01	0	0	0	0	6	1.6	0	0	0	0
Other beta-lactam (J01D)	Cefadroxil	J01DB05	13.5	4.5	0	0	0	0	0	0	0	0
Sulfonamides and trimethoprim (J01E)	Trimethoprim	J01EA01	0	0	0	0	4	1.04	0	0	0	0
	Sulfamethoxazole	J01EC01	0	0	0	0	4	1.04	0	0	0	0
	Sulfamethoxazole and trimethoprim	J01EE01	0	0	0	0	0	0	0	0	1	0.2
Lincosamides (J01FF)	Clindamycin	J01FF01	0	0	0	0	0	0	0	0	3	0.7
Aminoglycoside (J01G)	Amikacin	J01GB06	0	0	13.5	3.9	4.3	1.1	0	0	0	0
	Gentamicin	J01GB03	0	0	2.4	0.7	0	0	0	0	0	0
Watch (2)												
Other beta-lactam (J01D)	Cefuroxime	J01DC02	1	0.3	0	0	0	0	0	0	0	0
	Cefotaxime	J01DD01	0	0	0	0	9.8	2.5	0.5	0.2	0	0
	Ceftazidime	J01DD02	13.5	4.5	0	0	6	1.6	6	2.6	40.5	9.3
	Ceftriaxone	J01DD04	34.5	11.6	25	7.3	0	0	27	11.5	44	10.1
	Cefixime	J01DD08	3	1	0	0	0	0	0	0	1.5	0.3
	Cefoperazone	J01DD12	4.5	1.5	1.3	0.4	0	0	0	0	0	0
	Cefoperazone and sulbactam	J01DD62	0	0	24.8	7.2	6.8	1.8	0	0	0	0
Macrolide (J01FA)	Azithromycin	J01FA10	90	30.2	42.7	12.5	152.7	39.8	70	29.8	271.7	62.3
	Erythromycin	J01FA01	0	0	0	0	0	0	0	0	6	1.4
Quinolone (J01M)	Ciprofloxacin	J01MA02	0	0	0.3	0.1	0.5	0.1	0	0	0	0
	Levofloxacin	J01MA12	125	41.9	146.5	42.8	115.5	30.1	37.5	16	471	108
	Moxifloxacin	J01MA14	34	11.4	54	15.8	11	2.9	106	45.1	0	0
Reserve (3)												
Tetracycline (J01AA)	Tigecycline	J01AA12	0	0	27	7.9	0	0	0	0	0	0
Other beta-lactam (J01D)	Meropenem	J01DH02	88	29.5	140.8	41.2	12	3.1	30.3	12.9	3	0.7
Antimycotics for systemic use (J02)												
Triazole and tetrazole derivatives (J02AC)	Fluconazole	J02AC01	0	0	17	5	0	0	0	0	7.5	1.7
Other antimycotics for systemic use (J02AX)	Micafungin	J02AX05	0	0	36	10.5	0	0	0	0	0	0
Total			407	136.4	531.3	155.3	333.6	86.98	277.3	118.1	849.2	194.7
(b)												
Group	Name	ATC Code	Hospital A		Hospital B		Hospital C		Hospital D		Hospital E	
			DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days
Nucleosides and nucleotides excl. reverse transcriptase inhibitors (J05AB)	Aciclovir	J05AB01	0	0	0	0	0	0	0	0	0.8	0.2
	Remdesivir	J05AB16	84	28.2	213	62.3	44	11.5	33	14	158	36.2
Nucleotide and nucleotide reverse transcriptase inhibitors (J05AF)	Entecavir	J05AF10	0	0	0.3	0.9	0	0	0	0	0	0
Nuraminidase Inhibitors (J05AH)	Oseltamivir	J05AH02	47.5	15.9	23	6.7	0	0	3	1.3	110	25.2
Antivirals for treatment of HIV infections, combinations (J05AR)	Lopinavir and ritonavir	J05AR10	1.5	0.5	0	0	5	1.3	0	0	4	0.9
Other Antivirals (J05AX)	Inosine pranobex	J05AX05	0	0	0	0	0	0	7.7	3.3	0	0
	Favipiravir	J05AX27	17.3	5.8	88.5	25.9	146.1	38.1	38.6	16.4	19.8	4.5
Total			150.3	50.4	324.8	95.8	195.1	50.9	82.3	35	292.6	67

**Table 1.** *Cont.*

(c)												
Group	Name	ATC Code	RS A		RS B		RS C		RS D		RS E	
			DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days	DDD	DDD/100 Bed-days
Acetic acid derivatives and related substances (M01AB)	Diclofenac	M01AB05	0	0	0	0	0	0	0	0	6	1.4
Fenamates (M01AG)	Mefenamic acid	M01AG01	25.5	8.6	0	0	0	0	0	0	10.5	2.4
Total			25.5	8.6	0	0	0	0	0	0	16.5	3.8

The WHO’s AWaRe (access, watch, reserve) classification of antibiotics categorized antibiotics to the following: (1) Access group antibiotics that have activity against a wide range of commonly encountered susceptible pathogens; (2) Watch group antibiotics that have higher resistance potential; and (3) Reserve group antibiotics that were antibiotics of last resort when all alternatives have failed or are not suitable.

**2.1.2. Antivirus**

Unlike hospitals C and D, hospitals A, B, and E used remdesivir more often than favipiravir (Table 1b). The number of Remdesivir used in hospital B (62.3 DDD per 100 bed-days) is more than twice in hospital A (28.2 DDD per 100 bed-days). DDD Remdesivir injection (for parenteral use) is 0.1 g per day, whereas favipiravir is 1.6 g per day orally.

**2.1.3. Anti-Inflammatory Nonsteroid**

Only hospitals A and E give anti-inflammatory nonsteroid for COVID-19 patients with severe to critical conditions (Table 1c). The number of Mefenamic acid used in hospital A is more than twice in hospital E. The number of Mefenamic acid used in RS A was 25.5 DDD per 100 bed-days. This number implies that 25.5 out of 100 patients a day use 1 DDD Mefenamic acid (1 g) orally.

Overall, all hospitals use antibiotics (J01) more often than the antivirus (J05) (Table 1).

**2.2. Drug Effectiveness**

**2.2.1. Improving Patients’ Outcome During Hospitalization**

Among twenty-six drugs, the number of ceftazidime use is associated with the number of patients with better conditions (OR 0.16 [0.05–0.53]); so is dexamethasone (OR 3.95 [1.81–8.68]) and favipiravir (OR 2.14 [1.07–4.27]) (Table 2).

**Table 2.** Antiinfectives, antimycotics, anti-inflammatory, antivirals, and their effectiveness in improving patient outcomes during hospitalization.

Category	Level of Significance	Odds Ratio
		(Lower—Upper Bound at 95%)
J01DD02 (Ceftazidime)	0.002	0.16 (0.05–0.53)
J01DD04 (Ceftriaxone)	0.056	0.42 (0.17–1.02)
H02AB02 (Dexamethasone)	0.001	3.95 (1.81–8.68)
J05AH02 (Oseltamivir)	0.001	0.232 (0.09–0.56)
J05AX27 (Favipiravir)	0.03	2.14 (1.07–4.27)

**2.2.2. Length of Stay**

Heart problems ( $p = 0.023$ ) and obesity ( $p = 0.007$ ) were comorbidity factors that prolonged the patient’s length of stay. Age and gender association with length of stay was not significant (Table 3a).

**Table 3.** (a) Patients’ confounding factors and their relation to hospitalization outcome and length of stay. (b) Biochemical risk factors linking advanced age, cardiac comorbidities, and obesity to prolonged COVID-19 duration.

(a)		
	Standardized Coefficients	Level of Significance
<i>Factors for hospitalization outcome</i>		
Demographics		
Age	0.227	0.041
Comorbidities		
Heart	0.259	0.012
Immune	0.751	0.023
Respiration	0.275	0.01
Diabetes	1.979	0.055
Heart	2.375	0.023
Obesity	2.838	0.007
(b)		
Biochemical Marker	Pathophysiological Link to Comorbidities	Impact on COVID-19 Duration/Prognosis
IL-6 & CRP	Elevated baseline low-grade inflammation in obesity and age-related systemic “inflammaging”.	Triggers hyperinflammation and cytokine release syndrome, delaying recovery.
D-dimer	Chronic endothelial dysfunction in cardiac disease and prothrombotic state in obesity.	Increases macro/microvascular thrombotic events, necessitating extended therapeutic support.
Cardiac Troponin	Preexisting myocardial strain or subclinical ischemic damage in cardiac cohorts.	Signals virus-induced acute myocardial injury, compounding recovery challenges.
Fasting Glucose	Linked to insulin resistance and metabolic dysfunction common in obese populations.	Impairs early innate immune responses and prolongs viral shedding duration.

2.3. Potential Drug Repurposing Based on Its Structure

Target validation for the in silico molecular docking protocols relied on structural configurations characterized in established peer-reviewed literature. A dedicated reference matrix was synthesized to map the clinical rationale of matching the drug classes identified in the patient data against the three major therapeutic targets of SARS-CoV-2, as detailed in Table 4. Three PDB receptors targeted from the RCSB Protein Data Bank were 7D4F, 7T9L, and 7TLL. Methodological reliability was evaluated via native ligand re-docking replications, where a structural threshold of  $\leq 2.5 \text{ \AA}$  dictated protocol acceptance. The 7TLL receptor met the acceptance root-mean-square deviation (RMSD) criteria with an average value of  $0.8018 \text{ \AA}$  across three replications (Table 5). Conversely, 7D4F and 7T9L exceeded this validation threshold and were excluded from subsequent screening iterations.

**Table 4.** Literature validation and mechanisms for the clinical drug profiles against selected SARS-CoV-2 target proteins.

Drug Profile Class	Target Protein (PDB ID)	Mechanism and Biological Action Against the Receptor/Pathogenesis	Supporting Literature Evidence
Antivirals (e.g., Remdesivir, Lopinavir)	7D4F (RNA Polymerase) & 7TLL (Main Protease)	Direct inhibition of viral replication machinery; nucleoside analogs terminate RdRp synthesis while protease inhibitors disrupt polyprotein cleavage.	[14,15]
Antibiotics (e.g., Cefoperazone, Tigecycline)	7TLL (Main Protease)	Off-target computational affinity toward the catalytic dyad of Mpro; secondary management of severe bacterial co-infections in critical patients.	[16–18]
Anticoagulants (e.g., Rivaroxaban, Heparin)	7T9L (Spike Protein)	3 Competitive binding disruption at the receptor-binding domain (RBD) to prevent cell attachment; critical management of COVID-19 induced coagulopathy.	[19,20]
Corticosteroids (e.g., Budesonide, Dexamethasone)	Hyperinflammation Control (General Cellular Proximity)	Downregulation of systemic hyperinflammation and cytokine storms; indirect stabilization of host tissue damage during peak viral loads.	[21]

**Table 5.** Molecular docking program validation.

Receptor	RMSD Replication 1	RMSD Replication 2	RMSD Replication 3
7D4F	1.281	3.376	3.342
7T9L	3.432	4.289	4.522
7TLL	0.7529	0.7636	0.8887

Virtual screening with 7TLL receptors yielded 14 of 43 drug compounds with Gibbs free energy ( $\Delta G$ ) score  $-8.5$  to  $-10$  kkal/mol. A higher negative magnitude of the Gibbs free energy ( $\Delta G$ ) indicates a stronger thermodynamic affinity between the receptor macromolecule and the complexed ligand. Drug compounds potentially interacting with the 7TLL receptor for COVID-19 were drug compounds with a more negative  $\Delta G$  than the original ligand, namely: amikacin ( $\Delta G -8.6$  kkal/mol; antibiotic), remdesivir ( $\Delta G -8.8$  kkal/mol; antiviral), rivaroxaban ( $\Delta G -9.9$  kkal/mol; anticoagulant), and dexamethasone ( $\Delta G -8.7$  kkal/mol; corticosteroid).

### 3. Discussion

Within the cohort of 244 severe to critical COVID-19 patients, 62 individuals were over the age of 65. Advanced age and high scores on the Clinical Frailty Scale (CFS) serve

as significant predictors of morbidity [14]. These clinical outcomes are often linked to defective interferon production [15] and elevated levels of pro-inflammatory cytokines [22].

The selection of antibiotics varied across facilities; hospital C primarily utilized azithromycin, whereas other hospitals favored quinolones. Across all participating sites, antibiotics were prescribed more frequently than antivirals, a choice often made despite limited evidence supporting antibiotic effectiveness for this condition [23]. Frequently, the decision to initiate empiric antibiotic therapy is driven by inflammatory markers rather than disease severity or specific microbiology results [24,25]. Reviews of antibacterial use in COVID-19 indicate that, alongside azithromycin [26] and quinolones, cephalosporins also show a high prevalence of use [27]. Such high rates of usage are concerning, as they may increase the incidence of antibiotic resistance within the hospital environment [28].

In standard viral treatment, antivirals are typically reserved for severe or chronic states; however, in the context of COVID-19, these medications were also administered in mild cases [29]. Among the severe to critical patients in this study, remdesivir was utilized more often than favipiravir (Table 1b). Notably, only hospitals A and E provided nonsteroidal anti-inflammatory drugs to patients in these critical conditions (Table 1c). While ceftazidime, dexamethasone, and favipiravir were associated with specific patient outcomes (Table 2), the broader clinical evidence remains mixed. Some reviews fail to prove that antivirals significantly improve patient outcomes [30], while others report improved clinical status without a corresponding impact on mortality [31].

Cardiac comorbidities are major factors associated with both the necessity of hospitalization and the overall length of stay. Patients with underlying comorbidities generally experience longer hospitalizations [32] and face an increased risk of death [33]. The connection between heart disease and COVID-19 susceptibility is further influenced by using antihypertensives, such as ACE inhibitors and angiotensin receptor blockers, which are closely associated with ACE-2 receptor activity [34]. Beyond baseline pathophysiology, routine medications and altered pharmacokinetic profiles in these subgroups can actively prolong disease duration. While regular antihypertensives (ACEIs/ARBs) upregulate host ACE-2 expression, clinical consensus supports their continuation due to endothelial protective effects. However, polypharmacy in elderly patients increases drug–drug interaction risks with repurposed COVID-19 therapies, exacerbated by age-related declines in hepatic and renal clearance. Furthermore, obesity significantly expands the volume of distribution (Vd) for lipophilic medications [35]. This pharmacokinetic shift risks causing subtherapeutic tissue concentrations under standardized dosing regimens, thereby delaying viral or inflammatory clearance and directly extending the hospital length of stay noted in the studied cohort.

Beyond the primary protease framework, alternative molecular mechanisms offer broader pathways for small-molecule drug repositioning. The SARS-CoV-2 Orf3a viroporin channel represents a critical target involved in ion translocation, viral release, and the triggering of host cell apoptosis through NLRP3 inflammasome activation [36]. Computational drug repositioning against Orf3a could theoretically operate via distinct structural and pathophysiological modalities across the four clinical drug classes evaluated in this study. Small-molecule antivirals and antibiotics frequently possess complex hydrophobic ring structures capable of driving off-target structural alignment within the viroporin pore cavity, potentially blocking ion conductance and arresting downstream viral assembly. Concurrently, corticosteroids and anticoagulants provide indirect therapeutic synergy by actively counteracting the severe physiological damage induced by Orf3a-mediated cellular injury, specifically downregulating the resulting systemic hyperinflammation, cytokine storms, and localized hypercoagulability. While virtual screening in the present workflow was tightly confined to target macromolecules with fully co-crystallized native inhibitors

to ensure precise root-mean-square deviation (RMSD) validation, modeling the structural disruption of auxiliary targets like Orf3a presents a valuable horizon for maximizing multi-target drug repurposing strategies.

#### 4. Materials and Methods

The study was conducted in five private and public type B hospitals, referral hospitals, and advanced health care facilities, with the number of beds being 366, 235, 692, 231, and 225, respectively. This study collected the medical records of severe to critical COVID-19 patients who were treated in the intensive care room during the period from March 2020 to December 2021. During this timeframe, the dominant circulating SARS-CoV-2 strains transitioned from the ancestral wild-type to the Delta (B.1.617.2) variant, and the majority of the admitted cohort was unvaccinated or partially vaccinated due to early-phase national rollout timelines.

Patients were included if they had a laboratory-confirmed RT-PCR positive test and met the severity criteria upon admission. Individuals with incomplete core pharmacological records or a hospital stay of less than 24 h were excluded from the analysis. Individuals with severe illness were identified as individuals who had SpO<sub>2</sub> <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) <300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates >50%. Critical illness: individuals who had respiratory failure, septic shock, and/or multiple organ dysfunction. Treatment allocations—including antibiotics, antivirals, and corticosteroids—were entirely non-randomized and determined by attending physicians based on the contemporary national *Pedoman Tatalaksana COVID-19* guidelines. Patient data included gender, age, clinical spectrum, length of stay, and comorbidities.

Data on drug use, including type, dose, frequency, and duration of administration were collected. Drug consumption was quantified using the Defined Daily Dose (DDD) per 100 bed-days metric, where DDD represents the assumed average maintenance dose per day for a drug used for its main indication in adults, as defined by the WHO Collaborating Centre for Drug Statistics Methodology [37]. Patient data and drug use (DDD/100 bed days) were presented with tables and analyzed descriptively. Drug efficacy was investigated using a multiple logistic regression model to determine Odds Ratios (OR) for categorical hospitalization outcomes, alongside an Analysis of Covariate (ANCOVA) model to evaluate impacts on the continuous length of stay. Confounding variables such as patients' age, gender, COVID-19 severity, and categorized comorbidities were controlled in the model. Automatic weight correction was applied to the model to adjust for unbalanced outcome frequencies across the patient cohort. This ANCOVA framework incorporated the same confounding variables, such as age and comorbidities, used in the primary regression model. Model stability and validation were ensured by selecting predictor variables based on pre-established clinical relevance to maintain stable parameters within the sample size (n = 244). Multicollinearity among predictors was systematically evaluated and ruled out using Variance Inflation Factors (VIF < 3). Missing data were handled using a listwise deletion approach, ensuring only complete core clinical records were analyzed. Model assumptions and validation were verified via residual analysis and normality testing. The level of significance for all tests was set at 5%. All statistical analyses in this study were carried out using XLSTAT 2021.4.1.1199 (Addinsoft, Paris, France).

#### 5. Conclusions

Severe to critical COVID-19 patient therapy includes antibiotic, antiviral, anti-inflammatory steroids, and non-steroidal agents. There is no effective definitive causal drug to treat the virus. Ceftazidime, dexamethasone, and favipiravir are significantly associated

with patient outcomes within this retrospective cohort. Heart comorbidity is associated with prolonged length of stay. Of the forty-three drugs for COVID patients, dexamethasone is a drug that is associated with patient recovery and has a structure that has the potential binding affinity for the SARS-CoV-2 spike protein/protease. Further research is needed through randomized controlled trials to establish definitive targeted therapies against emerging coronavirus variants.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/covid6060103/s1>, Table S1: Baseline demographic inpatient COVID-19 ( $n = 244$ ).

**Author Contributions:** Conceptualization, H.W., R.Y., and F.H.; methodology, H.W. and F.H.; software, K.K.; validation, F.H., K.K., A. and H.W.; formal analysis, K.K. and A.; resources, A.K.J., S.K.O., D.R., and N.P.A.; data curation, K.K. and A.; writing—original draft preparation, H.W., R.Y., F.H., and K.K.; writing—review and editing, R.Y., F.H. and K.K.; visualization, K.K.; project administration, F.H.; funding acquisition, R.Y. All authors have read and agreed to the published version of the manuscript.

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