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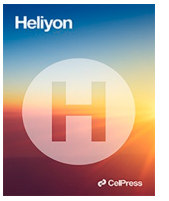

Inflammatory predictors (eosinophil, C-RP and IL-6) and effectiveness of oral Azvudine tablets treatment in COVID-19 hospitalized patients: A retrospective, self-controlled study

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ABSTRACT

Background: Although vaccinations and antiviral drugs are widely used in the clinical treatment worldwide, there is little investigation on the clinical outcomes and effectiveness of oral Azvudine tablets (FNC) treatment in COVID-19 hospitalized patients. The previous data showed Azvudine treatment was closely related to reduced virus shedding time, but the potential role of Azvudine on inflammatory response is scarce. Thus, this study is to investigate inflammatory predictors and effectiveness of oral Azvudine tablets treatment in COVID-19 hospitalized patients.

Methods: A total of 600 out of hospitalized patients were retrospectively collected over a 2-month period, of whom 60 out of hospitalized patients infected SARS-CoV-2. 32 of hospitalized patients who received Azvudine tablets were collected and the rest did not. Oral Azvudine tablets treatment: 5 mg/day for 7–14 days. We analyzed the routine blood tests, blood coagulation test, NT-proBNP, Troponin (cTNl), Creatine kinase MB (CK-MB) after oral Azvudine tablets treatment compared with that in before oral Azvudine tablets treatment. Also, we compared the CT chest and length of Stay after Azvudine treatment.

Results: We found that the number and percentage of eosinophil increased significantly, but the levels of C-reactive protein (C-RP) and IL-6 reduced remarkably after Azvudine treatment. In blood coagulation tests, the results showed that activated partial thromboplastin time (APTT) (mean ± SEM: 2.950 ± 2.268s) and fibrinogen (mean ± SEM: 0.8910 ± 0.5134g/L) down-regulated slightly, while there was similar in the level of D-Dimer (mean ± SEM: 0.1660 ± 0.3108 μg/mL) before and after Azvudine treatment. The expression of NT-proBNP reduced in Azvudine treatment (mean ± SEM: 897.1 ± 557.1pg/mL). Chest computed tomography (CT) scan reports also demonstrated that Azvudine treatment improved lung symptoms in COVID-19 hospitalized patients. Moreover, there is no difference in the average of length of stay in Azvudine treatment (the average of LOS days: 9.0) and no treatment (the average of LOS days: 9.0)

Conclusion: Oral Azvudine tablets treatment was associated with decreased inflammatory response and improved blood coagulation function, which should be substantial clinical benefits in COVID-19 hospitalized patients.

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1. Introduction

Coronavirus disease 2019 (COVID-19) has been a significant disease throughout the world in the past 3 years, and can exacerbate other conditions, such as diabetes, cardiovascular disease, and hypertension [1–3]. Vaccinations and antiviral drugs are widely applied in the clinical treatment of COVID-19 worldwide [4]. Real-world data have demonstrated that vaccines are highly effective against COVID-19, and have suggested a decreased number of patients suffering related severe disease and death. However, the effectiveness of vaccines may be reduced after receiving second or third dose [5,6]. Expert guidelines recommend antiviral drugs, such as Paxlovid [7] and Azvudine tablets, in the clinical use of COVID-19 [8,9]. In China, the clinical outcomes and effectiveness of oral Azvudine treatment in hospitalized patients with COVID-19 has not been well investigated. Azvudine (FNC, RO-0622), a first-in-class nucleoside-based prodrug developed by Henan Sincere Biotech Co., Ltd., was granted conditional marketing authorization by the National Medical Products Administration of China on July 25, 2022, and was the first Chinese oral SARS-CoV-2 RdRp inhibitor for treatment of adult patients with COVID-19. Furthermore, Azvudine is relatively inexpensive (US $40 or CN ¥270) per course and the mortality of patients with COVID-19 who have undergone Azvudine treatment is lower than that in control populations without Azvudine treatment [10].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients display a great variety of clinical characteristics and outcomes, such as long-term impact on pulmonary and multiple extrapulmonary tissues and organs [11]. C-reactive protein (C-RP) and interleukin (IL)-6 are important indicators in the evaluation of the degree of mild and severe diseases [12,13]. The level of eosinophil cells is reduced and gradually recovers to normal after optimal treatment of COVID-19, which could be a useful indicator for the degree of COVID-19 [14]. With regard to the effectiveness of Azvudine treatment, it not only contributes to reducing the viral shedding time [15,16], but is associated with lower risks of severe complications and all-cause-death in patients with COVID-19, especially in male patients [17]. A recent study showed that there was a sharp increase in alive $CD4^+$ and $CD8^+$ T cells in the thymus of monkeys after Azvudine treatment, which contributed to the improvement of immune cells functions in the thymus [18]. Additionally, coagulation function and cardiovascular variables are greatly changed in all patients with COVID-19, but data on the effect of Azvudine treatment on these parameters in hospitalized patients with COVID-19 are scarce. Therefore, further evidence of inflammatory predictors and of the effectiveness of Azvudine treatment in hospitalized patients with COVID-19 is urgently required.

In this retrospective study, we aimed to evaluate inflammatory predictors and the effectiveness of oral Azvudine tablet treatment in hospitalized patients with COVID-19 in Shenzhen Longhua District Hospital, which is the largest hospital situated in the northern region of Shenzhen, China.

2. Methods

2.1. Study design and treatment

This retrospective study was approved by the Ethics Review Committee of Shenzhen Longhua District Central Hospital in accordance with World Medical Association Declaration of Helsinki (WMA) (Ethical Application Ref: AF/SC-08/01.1/2023-044-01) and all written informed consent of the subjects have been included in the Ethics approval. A retrospective study was performed on COVID-19 patients over 18 years of age. A total of 600 out of hospitalized patients were retrospectively collected over a 2-month period, of whom 60 out of hospitalized patients infected SARS-CoV-2. 32 of hospitalized patients who received Azvudine tablets were collected and the rest did not. COVID-19 patients were treated with Azvudine Tablets 5 mg daily for 7–14 days.

2.2. Data collection

According to new Coronavirus Pneumonia Diagnosis and Treatment Program (version 10), COVID-19 patients were classified as asymptomatic, mild and severe. Demographic characteristics, patients' clinical characteristics, comorbidities, laboratory test results, chest computed tomography (CT) scan reports, echocardiogram and clinical outcomes were collected from medical patients' records. Laboratory test results consisted of routine blood tests, blood coagulation test, NT-proBNP, Troponin (cTNl), Creatine kinase MB (CK-MB) before and after oral Azvudine tablets treatment. The outcome of oxygen therapy and length of stay were collected from medical records. All results were checked by two separate medical researchers to confirm their accuracy.

2.3. Statistical analysis

The data on demographic and clinical characteristics of study patients is presented as frequency count (N) and percentages (%). The variables are reported as mean values ± standard error of mean (SEM) or Average. All statistical analyses are performed using GraphPad Prism 8.0 software (NIH, USA) and the two-tailed unpaired Student's *t*-test is used to calculate statistical differences between two groups. Patients with missing information for a given variable are excluded from the calculations/analysis. $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ are statistically significant.

3. Results

3.1. Patients' demographics and clinical characteristics

Sixty patients infected with SARS-CoV-2 who were hospitalized were included in this study; the average age of the patients was 65.8 years. A total of 72 % of the patients had received COVID-19 vaccines, and 28 % did not. The number of men with COVID-19 was higher than that of women with COVID-19 (56 % vs 44 %). With regard to comorbidities, hypertension was the most important co-morbidity (31 %). The rates of cardiac disease and diabetes were 31 % and 28 %, respectively. Additionally, half of the hospitalized patients with COVID-19 required oxygen supplementation. According to the new Coronavirus Pneumonia Diagnosis and Treatment Program (version 10), 75 % of the infections with SARS-CoV-2 were mild, which was the predominant group among hospitalized patients with COVID-19, while 19 % of patients with COVID-19 had severe symptoms. Fever (72 %) and cough (91 %) were the most obvious symptoms in hospitalized patients (Table 1).

3.2. Association between Azvudine treatment and inflammatory markers

Inflammatory markers are the most important indictors of inflammation in laboratory tests after SARS-CoV-2 infection. Reduced eosinophil expression [14], impaired lymphocytes [19], and elevated cytokine concentrations have been recorded in patients with COVID-19 [20], and Azvudine treatment reduces the inflammatory response and inhibits cytokine storms [18]. Azvudine treatment protects the thymus from SARS-CoV-2 damage and leads to elevated levels of lymphocytes ($CD3^+$, $CD4^+$, and $CD8^+$ cells), but not of CD 20+ cells, in Azvudine-treated monkeys [18], improving their immune cell function. Therefore, to investigate the effectiveness of Azvudine treatment, we analyzed the data on 32 hospitalized patients with COVID-19 before and after Azvudine treatment, and compared the inflammatory markers in these patients (Fig. 1). We found that the number (10^9/L) and percentage (%) of eosinophils were significantly higher ($P < 0.001$), and C-RP concentrations (mg/L) were remarkably lower after Azvudine treatment than before Azvudine treatment ($P < 0.001$), while the level of IL-6 (pg/ml) decreased ($P = 0.159$) (Fig. 2A, C, and D). The percentage and number of monocytes were similar before and after Azvudine treatment (Fig. 2B).

3.3. Association between Azvudine treatment and clinical outcomes

We also investigated the crude incidence rates of comorbidities, and found that hypertension (31 %) and cardiac disease (31 %) were the predominant diseases (Table 1). Laboratory blood coagulation tests showed that the activated partial thromboplastin time (APTT, mean ± standard error of the mean [SEM]: 2.950 ± 2.268 s) and fibrinogen concentrations (mean ± SEM: 0.8910 ± 0.5134 g/L) were slightly lower, while D-dimer concentrations (mean ± SEM: 0.1660 ± 0.3108 μg/mL) were similar, before Azvudine treatment compared with after Azvudine treatment (Fig. 2E–G).

The level of N-terminal pro B-type natriuretic peptide (NT-proBNP) was lower after Azvudine treatment than before treatment (mean ± SEM: 897.1 ± 557.1 pg/mL) (Fig. 2H). In contrast, Azvudine treatment was not associated with any change in cardiac

Table 1
Demographic and clinical characteristics of study patients.

Characteristics	Azvudine group
	N (%) (n = 32)
The mean of Age (29–94)	$\bar{x} = 65.8$
COVID-19 Vaccine	
Injection	23 (72)
No injection	9 (28)
Gender	
Male	18 (56)
Female	14 (44)
Comorbidities	
Diabetes	9 (28)
Hypertension	10 (31)
Cardiac disease	10 (31)
Need for oxygen supplementation	18 (56)
COVID-19 category	
Asymptomatic	2 (6)
Mild	24 (75)
Severe	6 (19)
Signs and symptoms	
Fever	23 (72)
Cough	29 (91)
Fatigue	1 (3)

Inflammatory markers (Eosinophil, C-RP and IL-6) and effectiveness of Oral Azvudine Tablets treatment in COVID-19 Hospitalized Patients: A Retrospective, Self-Controlled Study.

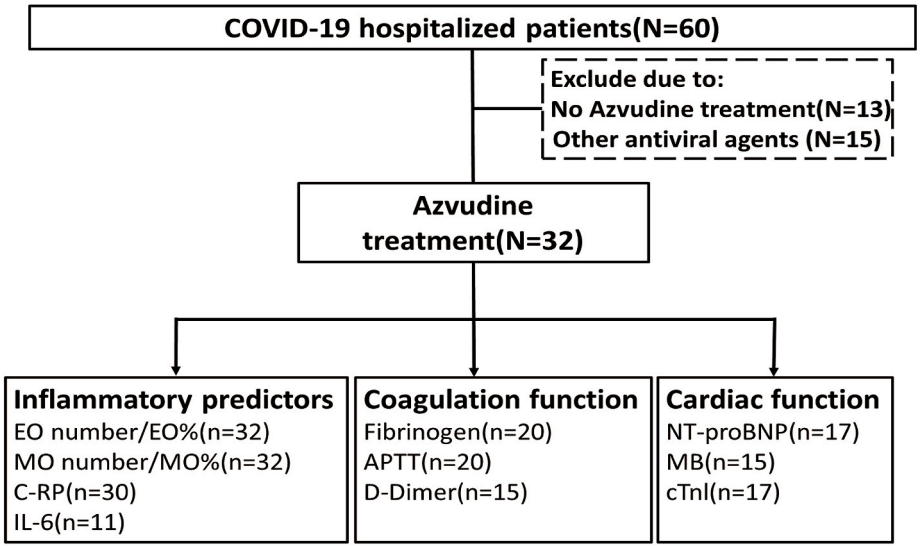

Fig. 1. The research design.

troponin I or creatine kinase MB concentrations (Fig. 2I and J). These results suggest that Azvudine treatment improved coagulation function and reduced NT-proBNP concentrations after SARS-CoV-2 infection. These changes may contribute to reducing the incidence rates of endothelial dysfunction and heart failure. Furthermore, chest computed tomography showed that Azvudine treatment improved lung symptoms in hospitalized patients with COVID-19 (Fig. 2K), but there was no difference between the average length of stay for Azvudine treated patients (average length of stay: 9.0 days) and non-treated patients (average length of stay: 9.0 days) (Fig. 2L).

4. Discussion

Since government policy and clinical expert guidelines recognized oral Azvudine treatment as a standardized treatment protocol for patients with COVID-19, Azvudine treatment has been widely used in China. Recent studies have shown that oral Azvudine treatment not only shortened the time to the first negative nucleic acid test results [15,16,21,22], but also reduced the risks of the accompanying disease progression outcome and all-cause death, especially for male patients with COVID-19 [6,17,23]. Additionally, Azvudine treatment improved the function of immune cells in monkeys [18]. Although Azvudine treatment is beneficial for patients with COVID-19, the evidence of inflammatory markers and for the effectiveness of Azvudine treatment is scarce.

A previous study showed that eosinophil expression was an important clinical index to evaluate COVID-19 progression, and that decreased eosinophils were related to worse infectious disease [14]. Our laboratory test results showed that the percentage and number of eosinophils were significantly increased after Azvudine treatment, which suggests the efficiency of Azvudine treatment in hospitalized patients with COVID-19. Moreover, Azvudine treatment reduced C-RP and IL-6 in these patients. This finding is consistent with previous studies, which showed improvement in COVID-19 symptoms and decreased C-RP and IL-6 concentration [24–26]. Therefore, the number of eosinophil, and C-RP and IL-6 concentrations may be effective and useful inflammatory markers in hospitalized patients with COVID-19 after oral Azvudine treatment.

SARS-CoV2 infection is closely related to endotheliitis, resulting in coagulation acceleration in endothelial cells [27]. High fibrinogen concentrations have been recorded in COVID-19. A study showed that fibrinogen concentrations in patients with severe COVID-19 were higher than those in patients with mild COVID-19 [28]. Also, abnormal APTT is common in COVID-19 sever patients and caused coagulation dysfunction [28]. In the present study, a slight decrease of APTT and fibrinogen concentrations was found in Azvudine treatment, and this result suggests that Azvudine treatment could be useful to COVID-19 sever patients in clinic. Increased D-dimer concentrations activate a coagulation response and promote systemic inflammatory response syndrome in patients with COVID-19 [29]. This finding indicates that D-dimer concentrations are a potential predictor for disease severity and mortality in patients with COVID-19 [30,31]. However, we found that there was no difference in D-dimer concentrations after Azvudine treatment compared with before treatment. NT-proBNP defined as a quantitative plasma biomarker reflecting haemodynamic cardiac stress in the diagnosis and administration of heart failure, pulmonary embolism and pneumonia [32,33]. Abnormal concentrations of NT-proBNP are associated with severe COVID-19 [34,35]. In our study, NT-proBNP concentrations were lower after Azvudine treatment than before Azvudine treatment, and our retrospective study suggested that Azvudine treatment is associated with reduced fibrinogen and NT-proBNP concentrations. Therefore, the number of eosinophil, and C-RP and IL-6 concentrations may be effective and useful inflammatory markers in hospitalized patients with COVID-19 after oral Azvudine treatment.

However, there were many limitations in our study. First, some out of hospitalized patients did not re-check body condition after Azvudine treatment, so parts of precious patients' information were missed. Second, SARS-CoV2 infection caused cytokine storm to

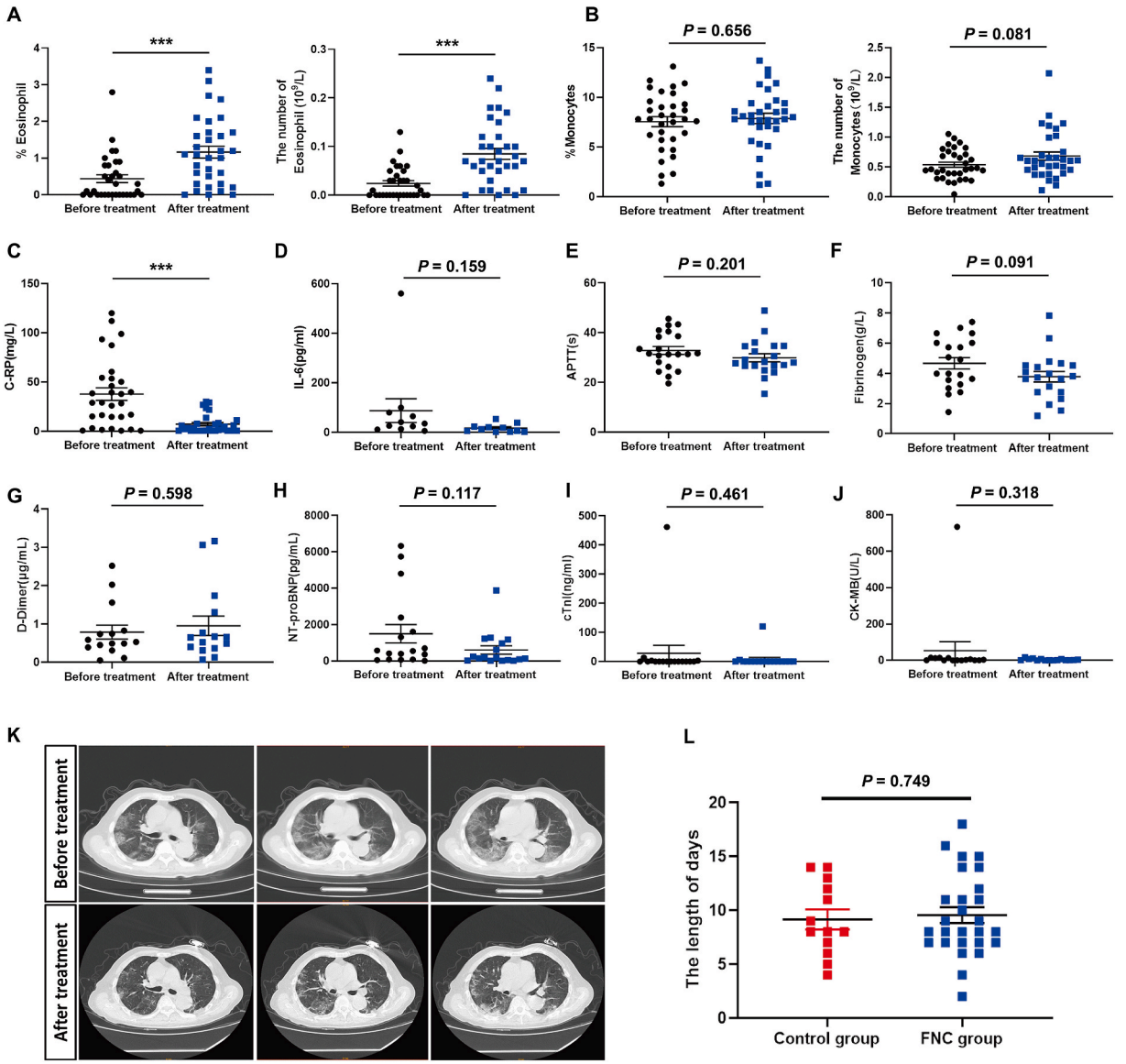

Fig. 2. Inflammatory predictors and effectiveness of Oral Azvudine Tablets treatment in COVID-19 Hospitalized Patients The serum level of **(A)** eosinophil, **(B)** monocytes, **(C)** C-reactive protein, and **(D)** IL-6 in COVID-19 hospitalized patients before and after Azvudine treatment; The serum level of **(E)** APTT, **(F)** fibrinogen, **(G)** D-Dimer, **(H)**NT-proBNP, **(I)** cTnl, and **(J)** CK-MB in COVID-19 hospitalized patients before and after Azvudine treatment; **(K)** the chest computed tomography (CT) scan report of a severe COVID-19 patient before and after Azvudine treatment; **(L)** The average of length of stay in control group and Azvudine treatment COVID-19 hospitalized patients (mean ± S.E.M, $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$).

induce severe inflammatory response in patients, but specific cytokines changes, such as interleukin family, TNF family and IFN family, did not check in COVID-19 patients with Azvudine treatment, Finally, a recent case report suggested that concomitant administration of Azvudine, warfarin, and rivaroxaban could increase international normalized ratio (INR) in a COVID-19 patient [36]. Thus, other potential predictors should be further considered when Azvudine and other drugs are concomitantly administered in COVID-19 patients.

5. Conclusion

Eosinophils, C-RP, and IL-6 may be useful inflammatory predictors to estimate the effectiveness of Azvudine treatment in the inflammatory response of patients with COVID-19. Fibrinogen and NT-proBNP appear to be effective for monitoring the progression of heart failure after Azvudine treatment in patients with COVID-19.

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Data availability statement

Data associated with the study has not been deposited into a publicly available repository and data will be made available on request.

CRediT authorship contribution statement

Yanli Zhao: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Validation, Writing – original draft, Writing – review & editing. **Gan Gao:** Data curation, Formal analysis, Investigation, Methodology, Validation, Conceptualization. **Wenhui Li:** Data curation, Formal analysis, Investigation, Methodology, Validation. **Zuqing Xu:** Formal analysis, Investigation, Methodology, Validation. **Xiao Wang:** Formal analysis, Investigation, Methodology, Validation. **Rong Chang:** Conceptualization, Formal analysis, Resources, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Y. Zhou, J. Chi, W. Lv, Y. Wang, Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19), Diabetes Metab Res Rev 37 (2) (2021) e3377.
[2] C.E. Dale, R. Takhar, R. Carragher, M. Katsoulis, F. Torabi, S. Duffield, S. Kent, T. Mueller, A. Kurdi, T.N. Le Anh, et al., The impact of the COVID-19 pandemic on cardiovascular disease prevention and management, Nat. Med. 29 (1) (2023) 219–225.
[3] M. Tadic, C. Cuspidi, G. Mancia, R. Dell'Oro, G. Grassi, COVID-19, hypertension and cardiovascular diseases: should we change the therapy? Pharmacol. Res. 158 (2020), 104906.
[4] T.C. Yip, G.C. Lui, M.S. Lai, V.W. Wong, Y.K. Tse, B.H. Ma, E. Hui, M.K.W. Leung, H.L. Chan, D.S. Hui, et al., Impact of the use of oral antiviral agents on the risk of hospitalization in community coronavirus disease 2019 patients (COVID-19), Clin. Infect. Dis. 76 (3) (2023) e26–e33.
[5] N. Andrews, E. Tessier, J. Stowe, C. Gower, F. Kirsebom, R. Simmons, E. Gallagher, S. Thelwall, N. Groves, G. Dabrera, et al., Duration of protection against mild and severe disease by covid-19 vaccines, N. Engl. J. Med. 386 (4) (2022) 340–350.
[6] J.J. Lau, S.M.S. Cheng, K. Leung, C.K. Lee, A. Hachim, L.C.H. Tsang, K.W.H. Yam, S. Chaothai, K.K.H. Kwan, Z.Y.H. Chai, et al., Real-world COVID-19 vaccine effectiveness against the Omicron BA.2 variant in a SARS-CoV-2 infection-naive population, Nat. Med. 29 (2) (2023) 348–357.
[7] J. Hammond, H. Leister-Tebbe, A. Gardner, P. Abreu, W. Bao, W. Wisemandle, M. Baniecki, V.M. Hendrick, B. Damle, A. Simon-Campos, et al., Oral nirmatrelvir for high-risk, nonhospitalized adults with covid-19, N. Engl. J. Med. 386 (15) (2022) 1397–1408.
[8] Y. Ye, China approves first homegrown COVID antiviral, Nature (2022).
[9] N. Murakami, R. Hayden, T. Hills, H. Al-Samkari, J. Casey, L. Del Sorbo, P.R. Lawler, M.E. Sise, D.E. Leaf, Therapeutic advances in COVID-19, Nat. Rev. Nephrol. 19 (1) (2023) 38–52.
[10] L. Yang, Z. Wang, Bench-to-bedside: innovation of small molecule anti-SARS-CoV-2 drugs in China, Eur. J. Med. Chem. 257 (2023), 115503.
[11] Z. Wang, L. Yang, Post-acute sequelae of SARS-CoV-2 infection: a neglected public Health issue, Front. Public Health 10 (2022), 908757.
[12] J.M. Michot, L. Albiges, N. Chaput, V. Saada, F. Pommeret, F. Griscelli, C. Balleyguier, B. Besse, A. Marabelle, F. Netzer, et al., Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report, Ann. Oncol. 31 (7) (2020) 961–964.
[13] Q. Li, X. Ding, G. Xia, H.G. Chen, F. Chen, Z. Geng, L. Xu, S. Lei, A. Pan, L. Wang, et al., Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: a retrospective case-control study, EClinicalMedicine 23 (2020), 100375.
[14] T. Mu, Z. Yi, M. Wang, J. Wang, C. Zhang, H. Chen, M. Bai, L. Jiang, Y. Zhang, Expression of eosinophil in peripheral blood of patients with COVID-19 and its clinical significance, J. Clin. Lab. Anal. 35 (1) (2021), e23620.
[15] B. Yu, J. Chang, Azvudine (FNC): a promising clinical candidate for COVID-19 treatment, Signal Transduct. Targeted Ther. 5 (1) (2020) 236.
[16] W. Chen, H. Xu, L. Hong, R. Yang, C. Peng, G. Wang, W. Li, Oral azvudine (FNC) tablets in patients infected with SARS-CoV-2 omicron variant: a retrospective cohort study, medRxiv (2023) 2023, 01.05.23284180.
[17] M. Shen, C. Xiao, Y. Sun, D. Li, P. Wu, L. Jin, Q. Wu, Y. Dian, Y. Meng, F. Zeng, et al., Real-world effectiveness of Azvudine in hospitalized patients with COVID-19: a retrospective cohort study, medRxiv (2023) 2023, 01.23.23284899.
[18] J.L. Zhang, Y.H. Li, L.L. Wang, H.Q. Liu, S.Y. Lu, Y. Liu, K. Li, B. Liu, S.Y. Li, F.M. Shao, et al., Azvudine is a thymus-homing anti-SARS-CoV-2 drug effective in treating COVID-19 patients, Signal Transduct. Targeted Ther. 6 (1) (2021) 414.
[19] B. Kudlinski, D. Zgola, M. Stolinska, M. Murkos, J. Kania, P. Nowak, A. Noga, M. Wojciech, G. Zaborniak, A. Zembron-Lacny, Systemic inflammatory predictors of in-hospital mortality in COVID-19 patients: a retrospective study, Diagnostics 12 (4) (2022) 859.
[20] N. Mangalmurti, C.A. Hunter, Cytokine storms: understanding COVID-19, Immunity 53 (1) (2020) 19–25.
[21] Z. Ren, H. Luo, Z. Yu, J. Song, L. Liang, L. Wang, H. Wang, G. Cui, Y. Liu, J. Wang, et al., A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study, Adv. Sci. 7 (19) (2020), e2001435.
[22] R.M. da Silva, P. Gebe Abreu Cabral, S.B. de Souza, R.F. Arruda, S.P.F. Cabral, A. de Assis, Y.P.M. Martins, C.A.A. Tavares, A.B. Viana Junior, J. Chang, et al., Serial viral load analysis by DDPCR to evaluate FNC efficacy and safety in the treatment of mild cases of COVID-19, Front. Med. 10 (2023), 1143485.
[23] G. Zeng, L. Wang, J. Li, Z. Zhang, Real-world effectiveness of Azvudine versus nirmatrelvir-ritonavir in hospitalized patients with COVID-19, J. Med. Virol. 95 (6) (2023), e28836.
[24] M. Milenkovic, A. Hadzibegovic, M. Kovac, B. Jovanovic, J. Stanisavljevic, M. Djikic, D. Sijan, N. Ladjevic, I. Palibrk, M. Djukanovic, , et al.C.R.P. D-dimer, PCT, and IL-6 levels at admission to ICU can predict in-hospital mortality in patients with COVID-19 pneumonia, Oxid. Med. Cell. Longev. 2022 (2022), 8997709.
[25] T. Herold, V. Jurinovic, C. Arnreich, B.J. Lipworth, J.C. Hellmuth, M. von Bergwelt-Baildon, M. Klein, T. Weinberger, Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19, J. Allergy Clin. Immunol. 146 (1) (2020) 128–136 e4.
[26] F. Liu, L. Li, M. Xu, J. Wu, D. Luo, Y. Zhu, B. Li, X. Song, X. Zhou, Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19, J. Clin. Virol. 127 (2020), 104370.

[27] Z. Varga, A.J. Flammer, P. Steiger, M. Haberecker, R. Andermatt, A.S. Zinkernagel, M.R. Mehra, R.A. Schuepbach, F. Ruschitzka, H. Moch, Endothelial cell infection and endotheliitis in COVID-19, Lancet 395 (10234) (2020) 1417–1418.
[28] Y. Zou, H. Guo, Y. Zhang, Z. Zhang, Y. Liu, J. Wang, H. Lu, Z. Qian, Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China, Biosci Trends 14 (4) (2020) 285–289.
[29] I. Leonard-Lorant, X. Delabranche, F. Severac, J. Helms, C. Pauzet, O. Collange, F. Schneider, A. Labani, P. Bilbault, S. Moliere, et al., Acute pulmonary embolism in patients with COVID-19 at CT angiography and relationship to d-dimer levels, Radiology 296 (3) (2020) E189–E191.
[30] Y. Yao, J. Cao, Q. Wang, Q. Shi, K. Liu, Z. Luo, X. Chen, S. Chen, K. Yu, Z. Huang, et al., D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study, J Intensive Care 8 (2020) 49.
[31] M. Rostami, H. Mansouritorghabeh, D-dimer level in COVID-19 infection: a systematic review, Expert Rev. Hematol. 13 (11) (2020) 1265–1275.
[32] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, V. Falk, J.R. Gonzalez-Juanatey, V.P. Harjola, E.A. Jankowska, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. J. Heart Fail. 18 (8) (2016) 891–975, 2016.
[33] J. Caro-Codon, J.R. Rey, A. Buno, A.M. Iniesta, S.O. Rosillo, S. Castrejon-Castrejon, L. Rodriguez-Sotelo, L.A. Martinez, I. Marco, C. Merino, et al., Characterization of NT-proBNP in a large cohort of COVID-19 patients, Eur. J. Heart Fail. 23 (3) (2021) 456–464.
[34] T. Guo, Y. Fan, M. Chen, X. Wu, L. Zhang, T. He, H. Wang, J. Wan, X. Wang, Z. Lu, Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19), JAMA Cardiol 5 (7) (2020) 811–818.
[35] L. Gao, D. Jiang, X.S. Wen, X.C. Cheng, M. Sun, B. He, L.N. You, P. Lei, X.W. Tan, S. Qin, et al., Prognostic value of NT-proBNP in patients with severe COVID-19, Respir. Res. 21 (1) (2020) 83.
[36] X. Zhang, F. Jiao, G. Li, X. Yu, Y. Pei, Y. Zhang, Z. Wang, P. Li, Elevated INR in a COVID-19 patient after concomitant administration of azvudine and anticoagulants, Front. Pharmacol. 14 (2023), 1191608.