American Journal of Cardiovascular Drugs (2022) 22:705–710
https://doi.org/10.1007/s40256-022-00547-4

ORIGINAL RESEARCH ARTICLE

Remdesivir-induced Bradycardia is not Associated with Worse Outcome in Patients with COVID-19: A Retrospective Analysis

Ioannis Pantazopoulos[1] · Georgios Mavrovounis[1] · Georgios Dimeas[1] · Nikolaos Zikos[1] · Maria Pitsikou[2] · Eleni Rousogianni[1] · Maria Mermiri[3] · Anastasia Michou[3] · Michalis Spanos[1] · Christos Maniotis[4] · Athanasios Chalkias[3] · Eleni Laou[3] · Georgios Zakynthinos[5] · Dimitrios Chatzis[6] · Konstantinos Gourgoulianis[2]

Accepted: 2 August 2022 / Published online: 25 August 2022

Abstract

Background COVID-19, is primarily a respiratory illness but is known to cause extrapulmonary manifestations, especially on the cardiovascular system. Bradycardia is commonly reported in COVID-19 patients despite no prior history of occurrence, and many studies have shown an association with increased mortality. Multiple case reports have been published showcasing remdesivir potentially causing bradycardia. Our aim was to investigate the incidence of bradycardia in patients receiving remdesivir and examine the association with disease severity and survival outcomes.

Methods A retrospective study was performed including 160 COVID-19 patients receiving remdesivir for 5 days. Patients' demographics, comorbidities, medication, vital signs, laboratory tests and outcome were recorded. Bradycardia was defined as a heart rate < 60 beats/min and severe bradycardia < 50 beats/min.

Results One hundred eighteen (73.8%) patients experienced at least one episode of bradycardia during hospitalisation. Bradycardia was present in 12 (7.5%) patients before treatment with remdesivir. The rate of bradycardia increased up to the 6th day of hospitalisation (40.6%) and subsequently diminished and normalised within 5 days after the last remdesivir dose (5% at Day 10). Severe bradycardia was observed in 13 (7.5%) patients. No difference was observed in ICU admission between groups (bradycardia vs no bradycardia). When we stratified patients according to the outcome of hospitalisation, no significant difference was observed in the occurrence of bradycardia between groups (alive vs dead) [$p = 0.853$].

Conclusions Treatment with remdesivir may be associated with new-onset bradycardia in hospitalised patients with COVID-19. However, bradycardia is transient and is not associated with ICU admission and mortality.

Key Points

Treatment with remdesivir may be associated with new-onset bradycardia in hospitalised patients with COVID-19.

Remdesivir-induced bradycardia is transient and not associated with ICU admission and mortality.

1 Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, in December 2019 and became a pandemic within a few months [1]. Coronavirus

✉ Ioannis Pantazopoulos
pantazopoulosioannis@yahoo.com

1 Department of Emergency Medicine, Faculty of Medicine, University of Thessaly, BIOPOLIS, 41500 Larissa, Greece

2 Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, BIOPOLIS, 41500 Larissa, Greece

3 Department of Anaesthesiology, Faculty of Medicine, University of Thessaly, BIOPOLIS, 41500 Larissa, Greece

4 Hygeia hospital, 151 23 Marousi, Athens, Greece

5 Third Department of Cardiology, Sotiria General Hospital, 11527 Athens, Greece

6 European University of Cyprus, Medical School, Nicosia, Cyprus

disease 2019 (COVID-19), is primarily a respiratory illness but is known to cause a wide array of extrapulmonary manifestations, especially on the cardiovascular system. Cardiac manifestations may include myocardial infarction, viral myocarditis and arrhythmias [2].

The pathophysiology of arrhythmogenesis is diverse, and myocardial injury, hypoxia, hypotension, enhanced inflammatory response, ACE-2 receptor down-regulation and/or medication may be implicated [3]. Bradycardia is commonly reported in COVID-19 patients despite no prior history of occurrence [4]. Several studies have shown that the onset of bradycardia in COVID-19 patients is associated with increased mortality [5, 6]. However, these studies did not include patients receiving remdesivir. Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase that was authorised by the Food and Drug Administration (FDA) for COVID-19 hospitalised patients and multiple case reports have been published showcasing remdesivir potentially causing bradycardia [7, 8]. The association between remdesivir-induced bradycardia and clinical outcome is not yet clear.

The aim of the present study was to investigate the incidence of bradycardia in patients receiving remdesivir and examine the association with disease severity and survival outcomes.

2 Methods

This retrospective study was approved by the Ethics Committee of our University Hospital (General University Hospital of Larissa, ID: 55944) and the requirement for informed consent was waived.

2.1 Study Subjects

Patients with COVID-19 pneumonia who were hospitalised between September 2020 and June 2021 were included in this retrospective analysis. Inclusion criteria were: (1) adult (aged ≥ 18 years) patients hospitalised primarily for COVID-19; (2) a confirmed SARS-CoV-2 infection diagnosed through reverse transcriptase polymerase chain reaction test of nasopharyngeal and/or oropharyngeal samples; (3) treatment including remdesivir. Patients with confirmed SARS-CoV-2 infection who were not primarily admitted for COVID-19 and patients with incomplete data were excluded.

All patients received oxygen supplementation therapy, dexamethasone, and low-molecular-weight heparin according to the recommendations of the National Institutes of Health (NIH) [9]. Remdesivir was administered according to the indications of the European Medicines Agency (EMA) as follows: 200 mg as loading dose on Day 1 and 100 mg on Days 2–5 [10]. All patients received remdesivir for a total of 5 days.

2.2 Data Collection

Patients' written and electronical medical records were reviewed. Data on demographics, comorbidities, Charlson Comorbidity Index (CCI), chronic medication, presenting day of illness since symptom onset, vital signs [blood pressure, heart rate, oxygen saturation (SpO_2) and fraction of inspired oxygen (FiO_2), temperature], laboratory studies [including white blood cells (WBC), ferritin, C-reactive protein (CRP), D-dimers], as well as medications and outcome were recorded during hospitalisation. All patients were classified following NIH severity classification at admission [11]. The electrocardiograms (ECGs) acquired on admission and during bradycardic episodes were reviewed to further characterise the bradycardia. Bradycardia was defined as a heart rate of < 60 beats/min and severe bradycardia as a heart rate of < 50 beats/min. Heart rates were collected three to six times per day according to patients' clinical status. Measurement of heart rate was not performed during sleep.

2.3 Statistical Analysis

Test of normality was performed to all numerical variables using the Shapiro-Wilk test. Numerical variables that followed normal distribution were presented as mean ± standard deviation (SD). For data not normally distributed, median with interquartile range (IQR) was used. The comparison between groups was performed using independent *t*-test. Categorical variables were presented as frequencies and percentages (*N*, %). Chi-square test (χ^2) was used to compare the clinical outcomes associated with bradycardia occurrence. *P*-values of <0.05 were considered statistically significant. All analyses were performed using the statistical software SPSS 22.0 (IBM Statistics).

3 Results

One hundred sixty patients were included with mean age 61.9 ± 16.48 years. Of them, 82 (51.3%) were men and 27 (16.9%) received antiarrhythmic drugs. The average time from the onset of symptoms was 6.78 ± 3.77 days. All patients had severe COVID-19 disease on admission, with median WBC, CRP, D-dimers, and ferritin on admission being 6.20 K/μL, 4.58 mg/dL, 285.00 μg/L, and 399.65 ng/mL, respectively.

3.1 Incidence of Bradycardia

Of the 160 patients, 118 (73.8%) experienced at least one episode of bradycardia during hospitalisation. Bradycardia was present in 12 (7.5%) patients before treatment with remdesivir. The rate of bradycardia increased up to the 6th day of hospitalisation (40.6%) and subsequently diminished and normalised within 5 days after the last remdesivir dose (5% at Day 10) [Fig. 1]. The fluctuation of the incidence of bradycardia remained the same even after excluding patients who were under treatment with antiarrhythmic drugs (Fig. 1). Severe bradycardia was observed in 13 (7.5%) patients of whom 7 were from the group of patients that presented with bradycardia before treatment with remdesivir. The lowest heart rate was 38 beats/min. All patients had sinus bradycardia. One patient had QT interval prolongation and two patients had first degree atrioventricular block. No case of haemodynamic instability was observed.

3.2 Comparison Between Groups According to Bradycardia Occurrence

No differences were observed regarding age, sex, SpO_2/FiO_2 on admission, SpO_2/FiO_2 on Day 6, antiarrhythmic drugs, WBC, CRP, CCI, D-dimers, ferritin and body temperature on admission and on Day 6 between patients with and without Day 6 bradycardia occurrence, as shown in Table 1.

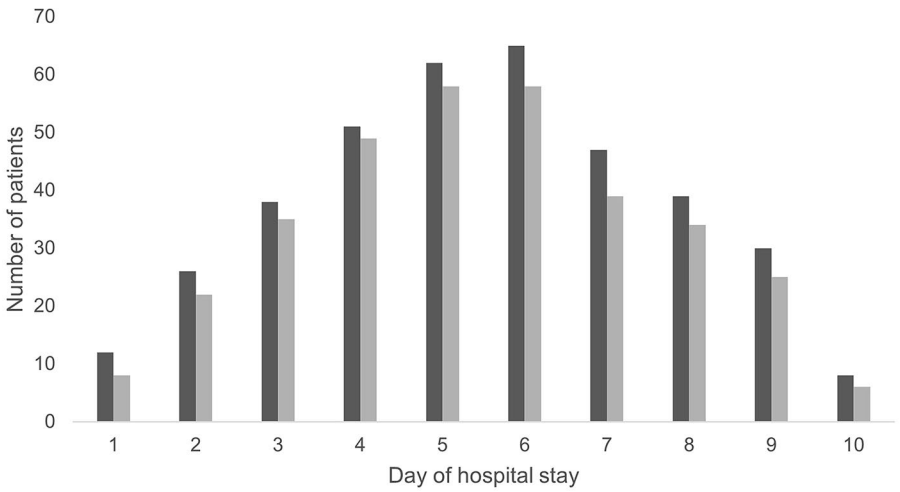

Fig. 1 Rate of bradycardia occurrence in patients receiving remdesivir (black) until Day 10 of hospital stay. Grey columns indicate patients who were not under chronic use of antiarrhythmic drugs

Table 1 Differences according to bradycardia occurrence at Day six of hospital stay

Day 6 of hospital stay			
Parameters	Bradycardia ($N=65$)	No bradycardia ($N=95$)	*P*-value
Age, years, mean ± SD	61.2 ± 14.7	62 ± 17.7	0.109
Male sex, *n* (%)	44 (67.7%)	60 (63.2%)	0.167
SpO_2/FiO_2 on admission, mean ± SD	277 ± 53.6	274.1 ± 50.7	0.626
SpO_2/FiO_2 on Day 6, mean ± SD	318.2 ± 67.6	314.9 ± 65.8	0.734
CCI, median (IQR)	4 (1–5)	4 (2–5)	0.163
Cardiovascular disease, *n* (%)	33 (50.7%)	44 (46.3%)	0.652
Antiarrhythmic drugs, *n* (%)	6 (13.3%)	21 (18.3%)	0.454
WBC, K/μL, median (IQR)	6.2 (5.40–9.00)	6.1 (4.85–7.95)	0.398
CRP, mg/dL, median (IQR)	4.28 (1.51–8.03)	4.77 (1.66–8.25)	0.346
D-dimers, μg/L, median (IQR)	250.00 (169.50–472.25)	311.55 (240.25–509.25)	0.381
Ferritin, ng/mL, median (IQR)	328.1 (90.70–900.30)	446.30 (239.80–768.00)	0.145
Body temperature on admission, °C, mean ± SD	36.5 ± 4.9	36.9 ± 0.8	0.119
Body temperature on Day 6, °C, mean ± SD	36.2 ± 0.5	36.2 ± 0.4	0.180

CCI Charlson Comorbidity Index, *CRP* C-reactive protein, *FiO_2* fraction of inspired oxygen, *IQR* interquartile range, *SD* standard deviation, *SpO_2* oxygen saturation, *WBC* white blood cells

3.3 Outcome

Mortality rate until the end of remdesivir administration on day 5 was significantly higher in the non-bradycardic group (3/42 vs 1/118, $p = 0.025$). When we stratified patients according to the outcome of hospitalisation, no statistically significant difference was observed in the occurrence of bradycardia between groups (alive vs. dead). Figure 2 shows cumulative survival according to the presence of bradycardia. In total, 6 (3.8%) patients were transferred to the intensive care unit (ICU) and 20 (12.6%) patients died. No case of sudden cardiac death was observed. From the six patients who were admitted in the ICU, three had bradycardia (50%). One patient from the bradycardia group and one from the non-bradycardic group finally died.

4 Discussion

The results of the present study demonstrate that bradycardia associated with remdesivir administration in COVID-19 hospitalised patients does not affect the course of the disease and is not associated with ICU admission or mortality.

Increasing evidence on the benefits of remdesivir in severe COVID-19 pneumonia has made the drug one of the most commonly prescribed medications during the pandemic. As a consequence, various side effects have been recognised. A recent study evaluating cardiovascular events and safety outcomes associated with remdesivir using a WHO international pharmacovigilance database reported that remdesivir was associated with cardiac arrest, bradycardia, and hypotension [12]. Although more research is needed regarding the mechanism of bradycardia after remdesivir infusion, several assumptions have been reported during the last two years. Some researchers support that remdesivir has a structural similarity with adenosine and acts on the sinus node causing bradycardia and conduction delay [13]. Others believe that remdesivir causes mitochondrial dysfunction and cardiotoxicity by affecting the human mitochondrial RNA polymerase, although its affinity towards viral RNA polymerase is > 500 times than human mitochondrial RNA polymerase [7]. Moreover, time-dependent worsening cytotoxic effects of remdesivir on cardiomyocytes infected with SARS-CoV-2 have been reported in an in vitro study at 24 and 48 h.

The incidence of bradycardia in our study (73.8%) is higher than that reported in previous studies (17–60%), which can be attributed to age, sex, temperature, severity, comorbidities, or even the definition of bradycardia [14–16]. For example, Palloto et al reported 47% of transient bradycardia defined as a heart rate < 60 beats/min in two consecutive measurements or a heart rate < 50 beats/min in one measurement. In our study, the incidence of bradycardia increased during the first five days of hospitalisation, reaching a peak 24 h after the last dose of remdesivir and returning to the pre-remdesivir levels at Day 10. Of note, several

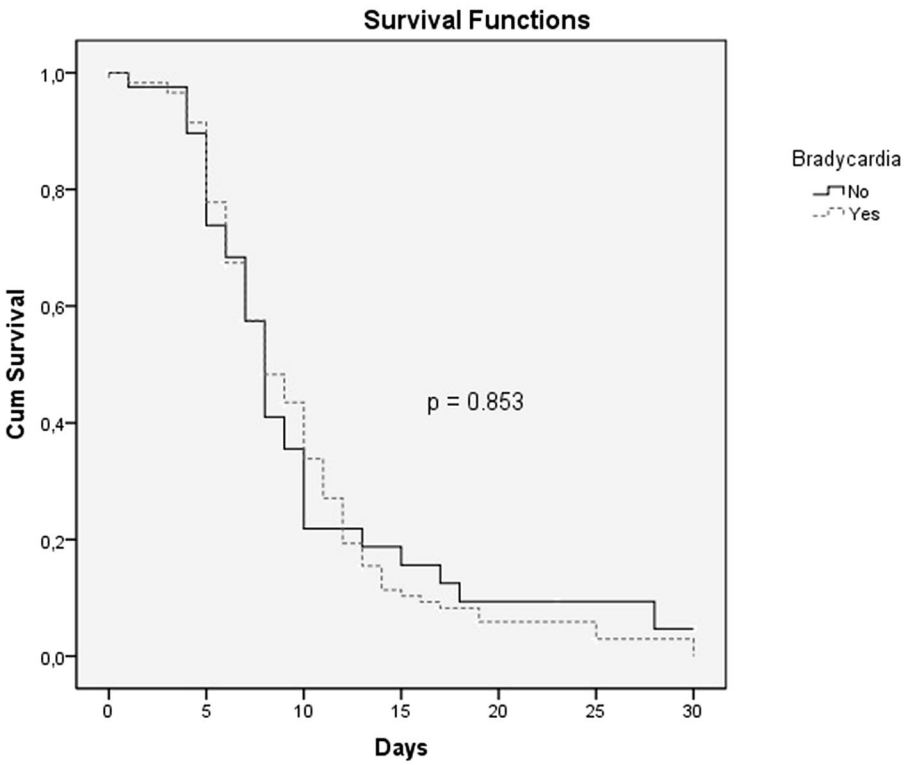

Fig. 2 Kaplan-Meier curves showing cumulative survival according to the presence of bradycardia

studies have reported that both symptoms and lung abnormalities on chest CT scans show greatest severity approximately 10 days after initial onset of symptoms [17, 18]. Since our patients were admitted after a median 6.78 days from the onset of symptoms, the peak of bradycardia overlaps not only with remdesivir administration but also with the peak of symptoms and radiological abnormalities. This raises the question of whether remdesivir or the severity of the disease is the cause of bradycardia. Since the severity of the disease is associated with the oxygen level [11], when we compared SpO_2/FiO_2 at Day 6 of hospitalisation, we found no significant difference compared to that of admission or that of patients without bradycardia.

An interesting result was that the mortality rate during the first 5 days of remdesivir administration was significantly higher in the non-bradycardic group, showcasing that remdesivir-induced bradycardia was not associated with worse mortality during the infusion period. Furthermore, when we stratified our patients according to the outcome of hospitalisation, we found that bradycardia was not associated with ICU admission or death. These observations are in accordance with previous studies [14, 15]. Interestingly, Bistrovic et al, suggested that the remdesivir-induced bradycardia might be associated with a favourable disease course due to the lack of a sympathetic-adrenergic cardiovascular stimulation that is often present in patients with respiratory deterioration [19]. Moreover, a matched case-control retrospective study suggested that if remdesivir is given during lower oxygen level requirements (before high-flow oxygen therapy or mechanical ventilation) it might be associated with improved survival in the subgroup of patients with atrial fibrillation [20]. This was attributed to both antiviral effects of the drug and improved heart rate control in patients with atrial fibrillation. However, it should be kept in mind that differences in patient population and proportion of specific subgroups might affect the observed results in different studies. In our study, all patients with remdesivir-induced bradycardia had sinus rhythm and a small number (7.6%) had severe bradycardia but without hemodynamic instability. Based on the available evidence and our results, all patients with remdesivir-induced bradycardia should be continuously monitored but physicians should not discontinue the drug in those who remain hemodynamically stable. Furthermore, physicians should keep in mind that the heart rate may normalise rapidly within 5 days after the last remdesivir dose. However, in case of deterioration and/or airway management, the potent adverse cardiovascular effects of remdesivir must be taken into account [21, 22].

We acknowledge that this is a single-centre study with a relatively small sample with a low rate of adverse events. Moreover, due to its retrospective nature, selection bias and misclassification or information bias may exist.

Treatment with remdesivir may be associated with new-onset bradycardia in hospitalised patients with COVID-19. In our study, bradycardia was transient and was not associated with ICU admission and mortality.

Declarations

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Ioannis Pantazopoulos, Georgios Mavrovounis, Georgios Dimeas, Nikolaos Zikos, Maria Pitsikou, Eleni Rousogianni, Maria Mermiri, Anastasia Michou, Michalis Spanos, Christos Maniotis, Athanasios Chalkias, Eleni Laou, Georgios Zakynthinos, Dimitrios Chatzis and Konstantinos Gourgoulianis declare that they have no potential conflict of interest that might be relevant to this work.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by IP, GM, GD, NZ, MP, ER, MM, AM, MS, CM, AC, EL, GZ, DC and KG. The first draft of the manuscript was written by Ioannis Pantazopoulos and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval General University Hospital of Larissa, ID: 55944

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to Participate Not applicable

Consent for Publication Not applicable

Code Availability Not applicable

References

1. Pantazopoulos I, Tsikrika S, Kolokytha S, Manos E, Porpodis K. Management of COVID-19 patients in the emergency department. J Pers Med. 2021;11:961.
2. AlShahrani I, Hosmani J, Shankar VG, AlShahrani A, Togoo RA, Yassin SM, et al. COVID-19 and cardiovascular system-a comprehensive review. Rev Cardiovasc Med. 2021;22:343–51.
3. Pandat S, Zhu Z, Fuentes-Rojas S, Schurmann P. Arrhythmias in COVID-19. Methodist DeBakey Cardiovasc J. 2021;17:73–82.
4. Amir M, Yoseph H, Farisi ATA, Phie JKP, Adam ATS. Symptomatic Bradycardia in Covid-19 hospitalized patients: a case series. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2021;111:1–4.
5. Kumar S, Arcuri C, Chaudhuri S, Gupta R, Aseri M, Barve P, et al. A novel study on SARS-COV-2 virus associated bradycardia as a predictor of mortality-retrospective multicenter analysis. Clin Cardiol. 2021;44:857–62.
6. Chalkias A, Pantazopoulos I, Papagiannakis N, Skoulakis A, Laou E, Kolonia K, et al. Sinus bradycardia is associated with poor outcome in critically ill patients with COVID-19 due to the B.1.1.7 Lineage. Toxicol Rep. 2021;8:1394–8.
7. Gubitosa JC, Kakar P, Gerula C, Nossa H, Finkel D, Wong K, et al. Marked sinus Bradycardia associated with remdesivir in COVID-19: a case and literature review. JACC Case Rep. 2020;2:2260–4.

8. Ching PR, Lee C. Remdesivir-associated bradycardia. BMJ Case Rep. 2021;14: e245289.
9. Hospitalized Adults: Therapeutic Management [Internet]. COVID-19 Treat. Guidel. [cited 2022 Feb 5]. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/
10. CZARSKA-THORLEY D. First COVID-19 treatment recommended for EU authorisation [Internet]. Eur. Med. Agency. 2020 [cited 2022 Jan 23]. Available from: https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation
11. Clinical Spectrum [Internet]. COVID-19 Treat. Guidel. [cited 2022 Feb 5]. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/
12. Jung SY, Kim MS, Li H, Lee KH, Koyanagi A, Solmi M, et al. Cardiovascular events and safety outcomes associated with remdesivir using a World Health Organization international pharmacovigilance database. Clin Transl Sci. 2021;2:2.
13. Zhang L, Zhou R. Structural basis of the potential binding mechanism of remdesivir to SARS-CoV-2 RNA-dependent RNA polymerase. J Phys Chem B. 2020;124:6955–62.
14. Attena E, Albani S, Maraolo AE, Mollica M, De Rosa A, Pisapia R, et al. Remdesivir-induced Bradycardia in COVID-19: a single center prospective study. Circ Arrhythm Electrophysiol. 2021;14: e009811.
15. Pallotto C, Blanc P, Esperti S, Suardi LR, Gabbuti A, Vichi F, et al. Remdesivir treatment and transient bradycardia in patients with coronavirus diseases 2019 (COVID-19). J Infect. 2021;83:237–79.
16. Pallotto C, Suardi LR, Gabbuti A, Esperti S, Mecocci L, Blanc P. Potential remdesivir-related transient bradycardia in patients with coronavirus disease 2019 (COVID-19). J Med Virol. 2021;93:2631–4.
17. Faes C, Abrams S, Van Beckhoven D, Meyfroidt G, Vlieghe E, Hens N, et al. Time between symptom onset, hospitalisation and recovery or death: statistical analysis of Belgian COVID-19 patients. Int J Environ Res Public Health. 2020;17:E7560.
18. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology. 2020;295:715–21.
19. Bistrovic P, Manola S, Lucijanic M. Bradycardia during remdesivir treatment might be associated with improved survival in patients with COVID-19: a retrospective cohort study on 473 patients from a tertiary centre. Postgrad Med J. 2021;2:2.
20. Bistrovic P, Manola S, Papic I, Jordan A, Ortner Hadziabdic M, Lucijanic M. Atrial fibrillation in COVID-19 patients receiving remdesivir, matched case-control analysis. Am J Emerg Med. 2022;S0735–6757(22):00281–9.
21. Russotto V, Myatra SN, Laffey JG, Tassistro E, Antolini L, Bauer P, et al. Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. JAMA. 2021;325:1164–72.
22. Chalkias A, Barreto EF, Laou E, Kolonia K, Scheetz MH, Gourgoulianis K, et al. A critical appraisal of the effects of anesthetics on immune-system modulation in critically ill patients with COVID-19. Clin Ther. 2021;43:e57-70.