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Remdesivir use in severe and critical COVID-19 patients might be associated with lower incidence of arterial thrombotic events

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ABSTRACT

Introduction: Venous thromboembolism (VTE) and arterial thrombotic (AT) events are a striking feature of severe COVID-19, however, relationship of remdesivir use and the risk of thrombotic events is unknown and has not been investigated before.
Methods: We retrospectively analyzed a cohort of 876 consecutive hospitalized severe and critical COVID-19 patients who were treated with remdesivir and compared them to 876 case-matched control patients. All patients were treated in our tertiary-level institution in period from 10/2020 to 6/2021. VTE and AT were diagnosed by objective imaging and laboratory methods.
Results: After exclusion of 71 VTE and 37 AT events present at the time of hospital admission, there were a total of 70 VTE (35 in the remdesivir and 35 in the control group) and 38 AT events occurring during hospitalization (13 in the remdesivir and 25 in the control group). There was a similar cumulative post-admission VTE incidence among both remdesivir and matched control patients ($P = 0.287$). Significantly lower cumulative post-admission AT incidence was observed among patients treated with remdesivir than among matched control patients (1.7% vs 3.3%, HR = 0.51, $P = 0.035$). Tendency for lower AT rates was evident in subgroups of patients stratified according to the type of AT, as well as according to the intensity of required oxygen supplementation at the time of remdesivir use.
Conclusion: Remdesivir use in severe and critical COVID-19 patients might be associated with lower occurrence of AT during hospitalization, whereas similar rates of VTE events were observed among both patients treated with remdesivir and control patients.

1. Introduction

Remdesivir is the first drug to be approved for treatment of severe or critical COVID-19 patients, and subsequently for patients who do not require oxygen therapy but are at risk of severe COVID due to prior comorbidities. Although initial approval was based on shortening of time to clinical recovery [1], post-marketing studies reported possible survival benefit among severe COVID-19 patients if requiring only low flow oxygen supplementation [2-4]. In addition, remdesivir use has been associated with cardiovascular side-effects such as bradycardia [5,6], hypotension, repolarization abnormalities and other [7]. Bistrovic et al. have suggested these phenomena might be associated with improved prognosis [6] and might contribute to favorable outcome of patients with cardiovascular comorbidities like atrial fibrillation [8]. Venous and arterial thrombotic events are a striking feature of severe COVID-19 [9], however, relationship of remdesivir use with the risk of thrombotic events is unknown and has not been investigated before. Thus, we aimed to compare the occurrence of

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venous thromboembolism (VTE) and arterial thrombotic (AT) events among patients hospitalized with COVID-19 who were treated with remdesivir with that among case-matched control patients from our large institutional registry.

2. Patients and methods

We retrospectively analyzed a cohort of 876 consecutive hospitalized COVID-19 patients who were treated with remdesivir and compared them to 876 case-matched control hospitalized COVID-19 patients. All patients were treated in a tertiary-level institution, University Hospital Dubrava, Zagreb, Croatia, from 10/2020 to 6/2021. COVID-19 severity was categorized at the time of hospital admission according to the World health organization (WHO) classification [10] as mild, moderate, severe and critical. All patients had either severe or critical intensity of symptoms at the time of remdesivir initiation. Remdesivir was given intravenously for five days to patients requiring oxygen supplementation up to fifteenth day from first onset of symptoms. The drug was given in the dose 200 mg intravenously on day one, followed by 100 mg intravenously daily for additional 4 days. Control patients were chosen among 5083 patients from the institutional registry who were not exposed to remdesivir, and were 1:1 matched based on age, sex, Charlson comorbidity index, COVID severity at the time of hospital admission and the level of oxygen requirement at the time of remdesivir institution. These variables were chosen for matching as they are known predictors of poor clinical outcomes in COVID-19 patients (age, sex, COVID-19 severity, comorbidity burden) and to account for the tendency to give remdesivir to respiratory deteriorating patients (level of oxygen requirement at the time of remdesivir use). Details on the matching procedure and clinical characteristics of investigated patients have been published previously [2]. Main reasons why comparable control patients did not receive remdesivir during study period are shortages of the drug, contemporary lack of unequivocal evidence of drug efficacy and safety, especially in elderly and comorbid patients, affecting clinical decision making of treating physicians and preferences of patients. Large majority of patients received low molecular weight heparins (LMWH) and corticosteroids of various dose intensity and duration per contemporary guidelines [11] and clinical judgement of treating physicians. Patients' characteristics and clinical outcomes were obtained from electronic and written medical records and are a part of hospital registry project (clinicaltrials.org identifier: NCT05151094). Patients who experienced VTE or AT immediately prior or at the time of hospital admission were excluded from the analysis of cumulative incidence of particular thrombotic events as presented in Fig. 1. Deep venous thrombosis (DVT) and pulmonary embolism (PE) were considered as VTE. Myocardial infarction (MI), cerebrovascular infarction (CVI) and peripheral arterial thromboses were considered as AT. All thromboses had to be proven by objective imaging and laboratory methods. For VTE, we only considered events that were proven by either color Doppler ultrasound or computerized tomography (CT) pulmonary angiography. For AT, we only considered events proven by either CT/angiography or significant laboratory increase in troponin judged by treating physician to be associated with acute coronary event and recorded in the medical documentation. No routine screening of asymptomatic patients with imaging methods at the time of hospital admission was performed. The study was approved by the University hospital Dubrava Review Board (nm. 2021/2503–04).

Numerical variables were tested for normality of distribution using the Shapiro-Wilk test. Due to non-normal distribution they were presented as median and interquartile range (IQR) and were compared using the Mann Whitney *U* test. Categorical variables were presented as frequencies and proportions and were compared using the chi-squared test. Cumulative incidence calculation was based on the Kaplan Meier method. Time to event curves were compared using the

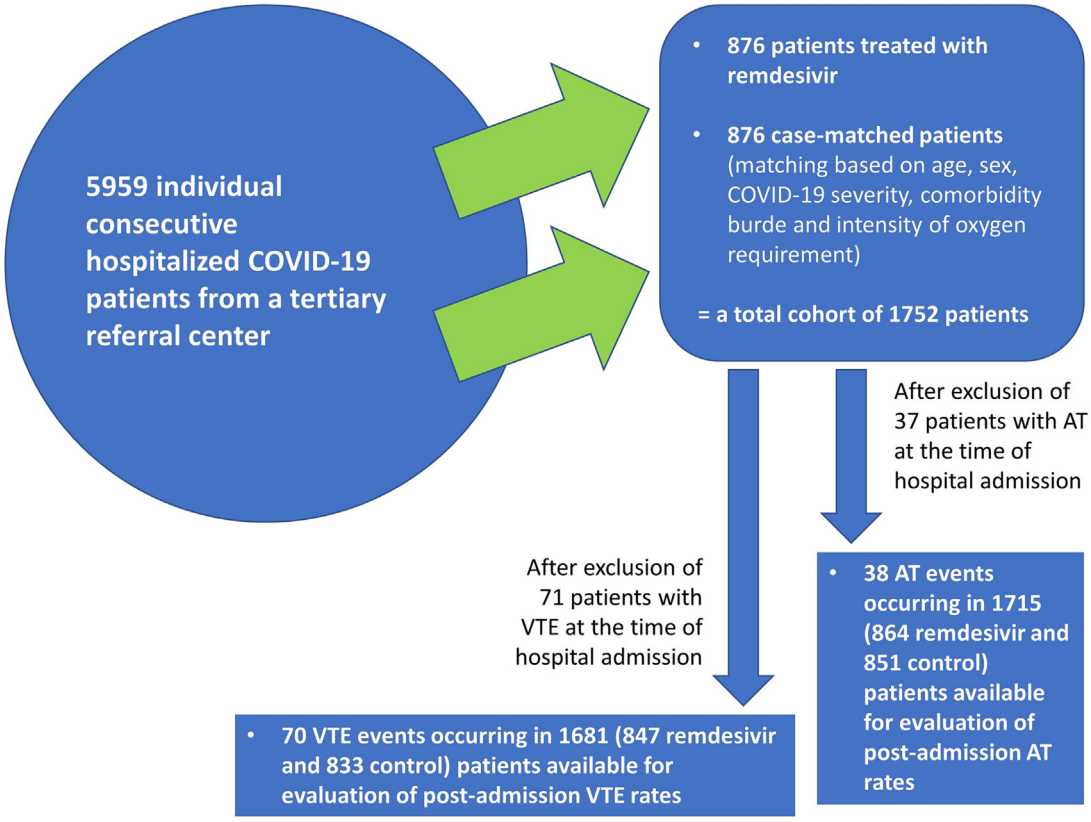

Fig. 1. Flow-chart of the study presenting patient selection process.

Cox-Mantel version of the log-rank test. *P* values <0.05 were considered as statistically significant. Initial screening of time-to-event associations was performed using the custom made MS Excel workbook [12]. All presented analyses were performed using the MedCalc statistical software version 20.114 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

Among a total of 1752 patients, median age was 66 years. Median Charlson comorbidity index was 3 points. A total of 61.8% of patients were of male sex, 80.2% had severe and 17.8% had critical severity of COVID-19 at the time of hospital admission. Patients' characteristics are shown in Table 1. Patients treated with remdesivir and control patients were balanced regarding matching parameters ($P > 0.05$ for all comparisons) [2].

With the exclusion of 71 VTE present at the time of hospital admission, there were a total of 70 VTE events occurring during hospitalization (35 in the remdesivir and 35 in the control group), including 34 DVT (21 vs 13) and 45 PE events (19 vs 26). Median time of VTE occurrence during hospitalization was 12.5 days, IQR (7–22). Cumulative post-admission VTE incidence was 0.9% at 30 days and 2.3% at 60 days in an entire cohort. There was a similar cumulative incidence of VTE events among both patients treated with remdesivir and matched control patients ($P = 0.287$) as shown in Fig. 2A.

With the exclusion of 37 AT present at the time of hospital admission, there were a total of 38 AT events occurring during hospitalization (13 in the remdesivir and 25 in the control group), including 8 MI (2 vs 6), 19 CVI (6 vs 13) and 11 peripheral AT events (5 vs 6). Median time of AT occurrence during hospitalization was 6.5 days from admission, IQR (4–13). Cumulative post-admission AT incidence was 2.4% at 30 and 60 days in an entire cohort. Significantly lower cumulative incidence of arterial thrombotic events was observed among remdesivir than among matched control patients (1.7% vs 3.1% at 30 days, HR = 0.51, $P = 0.035$) as shown in Fig. 2B. A tendency for lower AT rates was evident in subgroups of patients stratified according to the type of AT (MI, CVI, peripheral AT, Fig. 2C), as well as according to the intensity of required oxygen supplementation at the time of remdesivir use (Fig. 2D), although no statistical significance could be demonstrated due to low rates of events in particular subgroups.

4. Discussion

There are several important points we would like to emphasize. Our data suggest that remdesivir use in severe and critical COVID-19 patients might be associated with lower occurrence of AT events during hospitalization, whereas similar rates of VTE events were observed. Lower rates of AT events were consistently present in subgroups of patients requiring different intensity of oxygen supplementation, as well as for separate types of AT. To the best of our knowledge this is the first report of this clinical phenomenon.

Mechanisms of COVID-19 related thrombosis are incompletely understood. Venous and arterial thrombotic events in patients with severe/critical COVID-19 symptoms may develop despite prior exposure to even therapeutic doses of LWMH [9,13]. In-situ thrombotic events in proximal venous-blood circulation, like localized pulmonary artery thrombosis correlating with areas of pulmonary inflammation, are recognized as a feature of disease [14]. It is considered that immune mediated thrombo-inflammation and endothelial damage may play a central role in development of thrombotic events [15]. This view is supported by the decrease in pro-inflammatory and pro-coagulant profile of patients, as well as by lower occurrence of VTE in COVID-19 patients treated with dexamethasone [16], anti-inflammatory drug otherwise associated with known increased VTE risk [17]. 50% of AT and VTE events in our study were present at the time of hospital admission and were excluded from analyses. During hospitalization, AT tend to occur/ be detected earlier than VTE, possibly due to more clear clinical presentation of AT not overlapping with presentation of severe COVID-19 itself. VTE tend to be detected later, upon stabilization of patients who are not immediately able to undergo diagnostic procedures.

Although mechanistically unclear at the moment, our observation of lower AT rates among patients treated with remdesivir might be attributed to similarity of main remdesivir metabolites to adenosine [18]. Adenosine can cause vasodilatation and inhibition of platelet aggregation [19,20], and thus counteract mechanisms important in the pathogenesis of arterial thrombotic events. In addition, adenosine may ameliorate immune response and reduce the degree of inflammation [21,22]. A similar mechanism has been proposed for other observed adverse side effects of remdesivir, such as occurrence of bradycardia and higher propensity for bacterial infections [6,23]. Since a number of observed and potential cardiovascular side effects have been attributed to remdesivir use, and elderly and comorbid patients that encountered in typical real life situations have not been included into drug registration trials [7], clinicians may face a dilemma whether remdesivir use would be safe in respiratory deteriorating patients with cardiovascular comorbidities. Current findings, as well as previous works [8,24] support the role of remdesivir in this context.

Main limitations of our work are retrospective study design and low rate of investigated events in particular subgroups precluding further sub-analyses. Since large majority of patients were exposed to LMWH and corticosteroids in various duration and intensity, per contemporary guidelines for the treatment of severe COVID-19, we could not adequately control for these parameters and their potential contribution to occurrence of thrombosis. Since patients were not routinely screened using imaging techniques on admission, we can not exclude the possibility that some of earlier events were detected later during hospitalization as only symptomatic events recorded in the medical documentation were considered in the analysis. Main strengths of our work are large cohort of real-life patients treated with remdesivir and comparable control group chosen from a large pool of patients from the tertiary referral institution. Future studies of remdesivir and similar drugs are needed to better understand mechanisms behind our observations, as well as to define the place or remdesivir among other available drugs in COVID-19 patients.

Table 1
Clinical characteristics of patients treated with remdesivir and matched control patients.

	Remdesivir-treated ($N = 876$)	Matched controls (N = 876)	P value
Age (years), median and IQR	65 (56–74)	66 (57–74)	0.109
Sex			
Female	335 (38.2%)	335 (38.2%)	1.000
Male	541 (61.8%)	541 (61.8%)	
Charlson comorbidity index, median and IQR	3 (1–4)	3 (2–4)	0.114
COVID-19 severity			
Mild	8 (0.9%)	8 (0.9%)	0.829
Moderate	10 (1.1%)	10 (1.1%)	
Severe	695 (79.3%)	710 (81.1%)	
Critical	163 (18.6%)	148 (16.9%)	
HFOT	320 (36.5%)	326 (37.2%)	0.766
MV	249 (28.4%)	244 (27.9%)	0.791
ICU treatment	294 (33.6%)	310 (35.4%)	0.421

* Statistically significant at level $P < 0.05$. Abbreviations: IQR = interquartile range, HFOT = high flow oxygen therapy, MV = mechanical ventilation, ICU = intensive care unit.

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Authorship contributions

All authors contributed to the study conception and design.

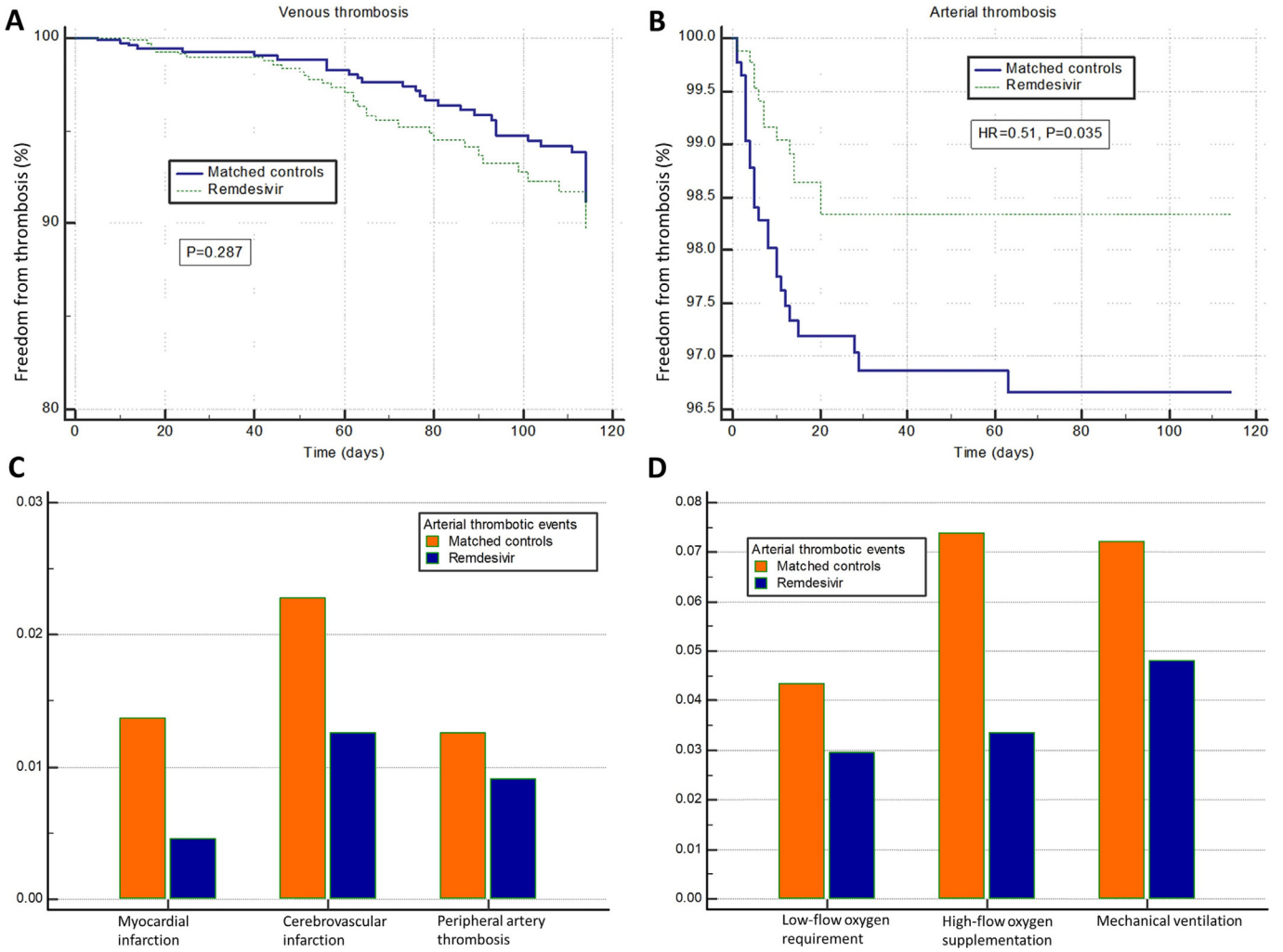

Fig. 2. Cumulative incidence of A) venous and B) arterial thrombotic events in patients treated with remdesivir and matched control COVID-19 patients. Time to event curves present thrombosis free rates over time, start at 100% thrombosis free rates and gradually drop with accumulation of thrombotic events. Rates of arterial thrombotic events stratified according to the C) type of arterial thrombosis and D) intensity of required oxygen supplementation at the time of remdesivir use.

Material preparation, data collection and analysis were performed by Petra Bistrovic, Ana Jordan, Iva Mihaljevic, Stela Bukvic, Stjepan Kovacevic, Darjan Ranilovic, Sara Sakota, Josipa Vlasac Glasnovic, Diana Delic-Brkljacic.

The first draft of the manuscript was written by Marko Lucijanic.

All authors read and approved the final manuscript.

Ethical approval

The study was approved by the University Hospital Dubrava Review Board (nm. 2021/2503-04).

CRediT authorship contribution statement

Marko Lucijanic: Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Petra Bistrovic:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Ana Jordan:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Iva Mihaljevic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Stela Bukvic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Stjepan Kovacevic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Darjan Ranilovic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Sara Sakota:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Josipa Vlasac Glasnovic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation. **Diana Delic-Brkljacic:** Writing – review & editing, Validation, Supervision, Methodology, Investigation.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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