Early 3-day course of remdesivir for the prevention of the progression to severe COVID-19 in the elderly: A single-centre, real-life cohort study

VASILIKI EPAMEINONDAS GEORGAKOPOULOU[1,2], AIKATERINI GKOUFA[1], SOTIRIA MAKRODIMITRI[1], DIMITRIOS BASOULIS[1,2], ARISTEIDIS TSAKANIKAS[1], GEORGIOS KARAMANAKOS[1], ELPIDA MASTROGIANNI[3], PANTAZIS M. VOUTSINAS[2], DEMETRIOS A. SPANDIDOS[4], CHRYSOVALANTIS V. PAPAGEORGIOU[3], MARIA N. GAMALETSOU[2,3] and NIKOLAOS V. SIPSAS[1,2]

[1]Department of Infectious Diseases and COVID-19 Unit, [2]Department of Pathophysiology, and [3]Emergency Department, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 11527 Athens; [4]Laboratory of Clinical Virology, School of Medicine, University of Crete, 71003 Heraklion, Greece

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Abstract. Remdesivir, a viral RNA polymerase inhibitor, has constituted a key component of therapeutic regimens against the pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Originally approved for administration in hospitalized patients, remdesivir leads to improved outcomes in patients with moderate to severe coronavirus disease 2019 (COVID-19). After proving to be effective in hospitalized patients, its use gained approval in early-stage disease for symptomatic outpatients who are at a high risk of progression to severe disease. The present study is a real-life prospective cohort study involving 143 elderly non-hospitalized patients with SARS-CoV-2 (≥65 years of age) who attended the emergency department of the authors' hospital seeking care for COVID-19 symptoms appearing within the prior 7 days. Eligible patients received intravenous remdesivir at a dose of 200 mg on the first day and 100 mg on days 2 and 3. The efficacy endpoints were set as the need for COVID-19-related hospitalization and all-cause mortality in the following 28 days. A total of 143 patients participated in the study. Of these patients, 118 (82.5%) patients were vaccinated with at least two doses. All patients enrolled completed the 3-day course, with a total of 6 out of 143 patients (4.2%) having a COVID-19-related hospitalization by day 28, and 5 patients (3.5%) succumbing to the disease within the study period. In the univariate Cox regression analysis, the neutrophil-to-lymphocyte ratio and haematological malignancy were identified as predictors of progression to severe disease, and albumin levels, the C-reactive protein-to-albumin ratio (CAR) and haematological malignancy were identified as predictors of 28-day mortality. On the whole, the findings of the present study demonstrated that among the elderly outpatients, a 3-day course of intravenous remdesivir was associated with favourable outcomes.

Correspondence to: Dr Vasiliki Epameinondas Georgakopoulou, Department of Infectious Diseases and COVID-19 Unit, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, 17 Agiou Thoma Street, 11527 Athens, Greece
E-mail: vaso_georgakopoulou@hotmail.com

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Introduction

Coronavirus disease 2019 (COVID-19) has affected >700 million individuals, resulting in more than six million deaths worldwide (https://covid19.who.int/). At the beginning of the pandemic, several drugs were used experimentally to manage this infection due to the emergency situation, and since then, numerous studies regarding treatment strategies have been conducted (1). Current management approaches for patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are based on the clinical course, the patient's risk factors and the availability of the agents (2).

The Food and Drug Administration (FDA) granted remdesivir as the first drug licensed for the treatment of severe COVID-19 (3). Remdesivir belongs to the nucleoside analogues and serves as a competitive inhibitor of viral RNA-dependent RNA polymerase, exhibiting a broad spectrum of action against various RNA viruses (4,5). Remdesivir, provided to adult patients hospitalized for COVID-19-associated pneumonia as a 10-day (6) or 5-day (7) course, shortens the recovery time and allows for early clinical improvement, according to phase 3 studies. In another study, remdesivir was shown to decrease the likelihood of patients requiring high-flow supplementary oxygen and invasive mechanical ventilation, as well as the risk of 14-day mortality, when compared to the placebo (8).

COVID-19 is responsible for disproportionately high rates of mortality among the elderly, particularly those with multiple comorbidities (9-12). According to the PINETREE study, a 3-day remdesivir course administered within 7 days following

symptom onset was found to be effective in decreasing the probability of hospitalization or mortality from any cause among outpatients who were at high risk of progression to severe disease due to comorbidities, including the elderly (13).

Apart from pivotal studies, limited real-world data supporting the effectiveness of early remdesivir therapy in decreasing the overall risk of hospitalization and disease progression in SARS-CoV-2 high-risk outpatients are currently available (14,15). In addition, real-life data focusing on the safety and effectiveness of early remdesivir among the elderly are limited. Considering the poor outcomes of COVID-19 in the elderly, providing real-world evidence on the safety and effectiveness of early remdesivir in this population is of utmost importance.

The present study aimed to assess the clinical features and outcomes of older adults (≥65 years of age) who received early remdesivir therapy in the outpatient setting during the predominance of the omicron variant of COVID-19.

Patients and methods

Study design. A single-centre prospective cohort study was conducted among consecutive SARS-CoV-2-infected elderly patients who received early remdesivir prophylactic therapy between January and October 2022. During the pandemic, Laiko General Hospital (Athens, Greece) was a national-level COVID-19 referral facility with a high-influx COVID-19 emergency department. The study was performed in accordance with the Declaration of Helsinki and obtained approval from the Institutional Review Board of Laiko General Hospital (protocol no. 765/12-2021). Written informed was obtained from all the study participants.

Inclusion criteria. Eligible patients were individuals ≥65 years of age who had mild/moderate SARS-CoV-2 infection confirmed by SARS-CoV-2 nasopharyngeal sample positivity using real-time polymerase chain reaction (RT-PCR) or antigenic testing. All eligible patients were enrolled sequentially at the time of evaluation at the emergency department, provided they agreed to receive remdesivir for a minimum of 3 days. The severity of COVID-19 was assessed based on the clinical spectrum of SARS-CoV-2 infection (https://www.covid19treatmentguidelines.nih.gov/).

Data collection. The data recorded were the following: i) age and sex; ii) comorbidities; iii) COVID-19 vaccination status; iv) disease course (onset of symptoms); v) nasopharyngeal SARS-CoV-2 RT-PCR and antigenic testing results; vi) laboratory parameters; vii) details of remdesivir treatment; viii) clinical outcomes. Baseline variables were recorded at the time of evaluation at the emergency department.

Therapeutic approaches. The included participants were administered 200 mg remdesivir *quaque die* (QD) intravenously and diluted in 0.9% saline following the manufacturer's recommendations (Gilead Sciences Ireland UC) followed by 100 mg remdesivir QD on the following 2 days. The protocol suggested 3 days of standard therapy. The outcomes were as follows: The primary endpoint was the progression to severe COVID-19 and the subsequent need for hospitalization. The secondary endpoint was all-cause mortality. All outcome measures were evaluated 28 days following the completion of remdesivir treatment.

Statistical analysis. Statistical analysis was performed using IBM SPSS-Statistics version 26.0 (IBM Corp.). Continuous variables are reported as the median with minimum-maximum ranges. Categorical variables are displayed as absolute numbers and percentages (%). The Kolmogorov-Smirnov test was used for determining the normality of the data. To identify predictors of event(s) (event=progression to severe disease or mortality at 28 days), statistically significant factors were examined using Cox proportional hazards univariate regression analysis. A two-sided P-value <0.05 was considered to indicate a statistically significant difference.

Results

In total, 143 patients (74 males, 51.7%) completed the prophylactic course and were enrolled during the research period, with a mean age of 77.38±8.29 years. The median time from symptom onset to the first dose of remdesivir was 1 day (range, 0-7 days). The median value of the Charlson Comorbidity Index (CCI) was 4 (range, 2-12). In total, 89 patients (62.2%) patients had >1 comorbidities. The most common comorbidities were arterial hypertension (65 patients, 45.5%) and cardiovascular disease, including ischemic stroke, acute myocardial infarction, coronary artery disease and arrhythmias (57 patients, 39.9%). Of the included patients, 118 (82.5%) patients were vaccinated with at least two doses. The characteristics of the study population are presented in Table I. No notable side-effects were observed from the prophylactic administration of remdesivir. In total, 6 patients (4.2%) were admitted to the hospital due to the progression of severe disease following the completion of the prophylactic course, and of these patients, 5 patients (out of 143 patients in total, 3.5%) succumbed to the disease within the study period. Of note, 4 patients succumbed due to COVID-19-associated pneumonia, 1 patient succumbed due to cardiac arrest after his hospitalization and 1 patient succumbed due to septic shock. As regards the risk factors for progression to severe disease and mortality among the non-survivors, 2 patients were suffering from haematological malignancy treated with B-cell depletion therapy, 1 patient was suffering from renal disease requiring haemodialysis, and the other 2 patients were unvaccinated.

In the univariate Cox regression analysis, the neutrophil-to-lymphocyte ratio [NLR; hazard ratio (HR), 0.522; 95% confidence interval (CI), 0.278-0.981; P=0.043] and haematological malignancy (HR, 6.667; 95% CI, 1.114-39.89, P=0.038) were identified as predictors of progression to severe disease (Table II), and the albumin levels (HR, 0.806; 95% CI, 0.689-0.942, P=0.007), C-reactive protein-to-albumin ratio (CAR; HR, 1.768; 95% CI, 1.019-3.069; P=0.043] and hematological malignancy (HR, 0.150; 95% CI, 0.025-0.898; P=0.038) were identified as predictors of 28-day mortality (Table III).

The demographic characteristics and the levels of laboratory parameters of the patients who succumbed and the patients who were alive at 28 days are presented in Table IV.

Table I. Characteristics of the study population.

Parameter	Value
Age (years), mean ± SD	77.38±8.29
CCI, median (range)	4 (2-12)
Sex, n (%)	
Female	69 (48.3)
Male	74 (51.7)
Comorbidities, n (%)	
None	15 (10.5)
Respiratory disease (COPD, asthma, ILD, OSA)	9 (6.3)
Obesity	3 (2.1)
Diabetes mellitus	31 (22)
Arterial hypertension	65 (45.5)
Cardiovascular disease (ischemic stroke, arrhythmia, coronary artery disease, myocardial infarction)	57 (39.9)
Heart failure	12 (8.4)
Autoimmune disease	11 (7.7)
Haematological malignancy	13 (9.1)
Solid malignant neoplasm	4 (2.8)
Renal disease	30 (21.1)
Solid organ transplantation	18 (12.6)
Vaccination status, n (%)	
Unvaccinated	25 (17.5)
Vaccinated with two doses	53 (37.1)
Vaccinated with at least three doses	65 (45.4)
Progression to severe disease	6 (4.2)
Mortality within 28 days	5 (3.5)

CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; OSA, obstructive sleep apnoea; SD, standard deviation.

Discussion

In the PINETREE study, the probability of COVID-19-associated hospitalization or all-cause mortality was 87% lower in the remdesivir group compared to the placebo group during the first 7 days from symptom onset and with at least one underlying risk factor for progression to severe disease (13). Obesity, cardiovascular or cerebrovascular illness, diabetes mellitus, hypertension, immunodeficiency, mild or moderate chronic renal disease, chronic liver and respiratory disease, malignancy, or sickle cell disease were all considered risk factors in the PINETREE trial. However, diabetes mellitus, obesity and hypertension were identified as risk factors in the vast majority of enrolled individuals (62, 55 and 48%, respectively). The exclusion of vaccinated individuals, as well as the lack of patients with non-omicron variants, were the main limitations of that study that limited its applicability in everyday clinical practice (13).

Currently, a limited number of real-life studies have demonstrated that the early administration of remdesivir has a good safety profile and significantly reduces the risk of COVID-19 disease progression and mortality among high-risk patients in the era of the omicron variant (14,16-18). A recent study focused on non-hospitalized vaccinated high-risk patients and demonstrated that a 3-day course of remdesivir resulted in a 75% lower possibility of hospitalization and 95% of respiratory failure, with favourable outcomes in cases that required hospitalization (19). Previous studies have reported that an early 3-day course of remdesivir has an outstanding safety profile and may prevent disease progression among elderly patients infected with SARS-CoV-2 during hospitalization in palliative care and internal medicine wards (20,21). To the best of our knowledge, this is the first study focusing on real-life data from elderly outpatients with SARS-CoV-2 infection treated with a 3-day early course of remdesivir during the surge of the omicron variant. The results obtained from the 3-day early course of remdesivir in the present study cohort were notable, considering that during the predominance of the omicron variant, the majority of severe cases and in-hospital deaths occurred among individuals aged >65 years (22).

Recent studies have reported that early remdesivir treatment in solid organ transplant recipients is linked to a lower probability of hospitalization and/or mortality (18,23). Of note, in the presenst study, no disease progression or mortality was observed among elderly solid organ transplant recipients. This finding supports the findings of previous research indicating that immunosuppressive drugs used in solid organ

Table II. Univariate Cox-regression analysis (outcome: Progression to severe disease).

			95% CI	
Variable	P-value	HR	Lower	Upper
Age (years)	0.504	0.971	0.889	1.059
CCI	0.390	0.765	0.415	1.410
Hb (g/dl)	0.632	0.900	0.585	1.384
Hct (%)	0.791	0.979	0.839	1.143
WBC (K/μl)	0.681	0.947	0.733	1.225
Neu (K/μl)	0.607	0.923	0.680	1.253
Lym (K/μl)	0.910	1.066	0.351	3.234
IGs (10^9/l)	0.986	0.894	0.001	26.202
PLTs (K/μl)	0.609	0.997	0.984	1.010
d-Dimers (μg/ml)	0.702	1.055	0.802	1.387
FIB (mg/dl)	0.999	1.000	0.993	1.007
Creatinine (mg/dl)	0.721	1.049	0.807	1.363
AST (U/l)	0.466	0.964	0.874	1.064
ALT (U/l)	0.836	0.992	0.918	1.071
ALP (U/l)	0.531	0.992	0.968	1.017
GGT (U/l)	0.478	0.977	0.918	1.041
LDH (U/l)	0.509	1.001	0.997	1.006
CRP (mg/l)	0.466	0.992	0.969	1.014
Fer (ng/ml)	0.436	0.988	0.959	1.018
Alb (g/l)	0.988	1.002	0.772	1.300
NLR	0.043	0.522	0.278	0.981
PLR	0.067	0.987	0.974	1.001
CAR	0.547	1.267	0.587	2.733
Male sex	0.193	4.290	0.479	38.38
Full vaccination	0.108	4.333	0.724	25.93
Respiratory disease (COPD, asthma, ILD, OSA)	0.703	22.182	0.001	18.63
Obesity	0.828	20.738	0.001	148.65
Diabetes mellitus	0.464	0.034	0.001	292.04
Arterial hypertension	0.807	0.800	0.134	4.788
Cardiovascular disease (ischemic stroke, arrhythmia, coronary artery disease, myocardial infarction)	0.383	0.377	0.042	3.375
Heart failure	0.369	2.729	0.305	24.41
Autoimmune disease	0.673	0.044	0.001	886.88
Haematological malignancy	0.038	6.667	1.114	39.89
Solid malignant neoplasm	0.801	0.048	0.001	92.71
Renal disease	0.951	0.933	0.104	8.35
Solid organ transplantation	0.586	0.041	0.001	417.29

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; COPD, chronic obstructive pulmonary disease; Fer, ferritin; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, haemoglobin; Hct, haematocrit; IGs, immature granulocytes; ILD, interstitial lung disease; LDH, lactate dehydrogenase; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; Neu, neutrophils; OSA, obstructive sleep apnoea; PLTs, platelets; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell.

transplantation may have a beneficial anti-inflammatory role and that the greater likelihood of COVID-19 progression in these individuals may be driven by other comorbidities, such as cardiovascular disease and diabetes mellitus (24,25).

According to a recent study on patients with haematological malignancies treated with various therapies, early treatment with remdesivir was associated with a failure rate of 3.4% (3/59 patients) (26). In the present study, among the elderly

Table III. Univariate Cox-regression analysis (outcome: 28-day mortality).

Variable	P-value	HR	95% CI	
			Lower	Upper
Age (years)	0.149	1.067	0.977	1.166
CCI	0.181	1.290	0.889	1.874
Hb (g/dl)	0.898	1.030	0.653	1.625
Hct (%)	0.825	0.983	0.846	1.143
WBC (K/μl)	0.681	0.938	0.690	1.274
Neu (K/μl)	0.432	0.866	0.604	1.241
Lym (K/μl)	0.080	2.127	0.913	4.955
IGs (10^9/l)	0.947	1.193	0.007	21.706
PLTs (K/μl)	0.343	0.994	0.982	1.006
d-Dimers (μg/ml)	0.125	1.209	0.949	1.540
FIB (mg/dl)	0.123	1.005	0.999	1.011
Creatinine (mg/dl)	0.152	1.275	0.915	1.776
AST (U/l)	0.429	1.017	0.976	1.059
ALT (U/l)	0.277	1.025	0.981	1.070
ALP (U/l)	0.677	0.993	0.963	1.025
GGT (U/l)	0.644	0.990	0.951	1.032
LDH (U/l)	0.760	1.001	0.997	1.004
CRP (mg/l)	0.140	1.012	0.996	1.029
Fer (ng/ml)	0.060	1.002	1.000	1.003
Alb (g/l)	0.007	0.806	0.689	0.942
NLR	0.136	0.742	0.501	1.098
PLR	0.129	0.992	0.982	1.002
CAR	0.043	1.768	1.019	3.069
Male sex	0.932	0.932	0.188	4.620
Full vaccination (three doses)	0.194	2.889	0.583	14.313
Respiratory disease (COPD, asthma, ILD, OSA)	0.703	0.045	0.001	36.524
Obesity	0.828	20.73	0.001	14.746
Diabetes mellitus	0.464	29.56	0.003	25.812
Arterial hypertension	0.282	3.333	0.373	29.821
Cardiovascular disease (ischemic stroke, arrhythmia, coronary artery disease, myocardial infarction)	0.311	46.02	0.028	76.265
Heart failure	0.369	0.366	0.041	3.275
Autoimmune disease	0.673	22.68	0.001	45.964
Haematological malignancy	0.038	0.150	0.025	0.898
Solid malignant neoplasm	0.801	20.96	0.001	40.263
Renal disease	0.951	1.07	0.120	9.583
Solid organ transplantation	0.586	24.68	0.001	25.212

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson comorbidity index; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; COPD, chronic obstructive pulmonary disease; Fer, ferritin; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, haemoglobin; Hct, haematocrit; IGs, immature granulocytes; ILD, interstitial lung disease; LDH, lactate dehydrogenase; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; Neu, neutrophils; OSA, obstructive sleep apnoea; PLTs, platelets; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell.

patients with haematological malignancies, the failure rate of early remdesivir administration was 15.4% (2/13 patients). In addition, two of the five deaths (40%) occurred in patients with haematological malignancies under B-cell depletion therapy. The continuing pandemic is a serious concern for patients treated with B-cell depletion therapy who exhibit clinical and virological evidence of SARS-CoV-2 infection that lasts >21 days and/or more than two episodes of acute

Table IV. Demographics and the levels of laboratory parameters in patients who succumbed and in patients who were alive at 28 days.

	Mortality within 28 days	
Parameter	Yes	No
Age (years), mean ± SD	81.80±12.27	77.33±8.21
Hb (g/dl), mean ± SD	12.26±2.44	12.30±1.75
Hct (%)	36.16±6.75	37.10±5.21
WBC (K/μl)	5.68±4.43	6.76±2.71
PLTs (K/μl)	152.40±75.57	194.64±70.74
FIB (mg/dl)	525.00±174.05	463.20±135.55
CCI, median (range)	5 (3-7)	4 (2-12)
Lym (K/μl), median (range)	1.53 (1.04-2.79)	0.980 (0.06-3.80)
Neu (K/μl), median (range)	2.60 (0.20-9)	4.30 (0.06-14.40)
IGs (109/l)	0.04 (0.03-014)	0.03 (0.01-1.31)
d-Dimers (μg/ml), median (range)	1.22 (0.23-9.51)	0.74 (0.10-2.87)
Creat (mg/dl), median (range)	0.75 (0.62-9.78)	1.08 (0.31-7.86)
AST (U/l), median (range)	23 (17-78)	22 (10-98)
ALT (U/l), median (range)	26.50 (11-45)	14 (12-81)
ALP (U/l), median (range)	81.50 (43-129)	68.50 (25-332)
GGT (U/l), median (range)	19 (22-47)	20 (15-157)
LDH (U/l), median (range)	294.50 (197-340)	224.00 (92-1,949)
CRP (mg/l), median (range)	38.74 (2.7-79.16)	18.19 (1.19-157.71)
Fer (ng/ml), median (range)	780 (12-1,560)	168.50 (14-1,997)
Alb (g/l), median (range)	35.35 (28.8-37.5)	41,500 (26.1-72.6)
NLR	1.21 (0.13-3.23)	4.30 (0.51-56.7)
PLR	69.53 (45.88-244.23)	177 (5.54-2050)
CAR	1.26 (0.07-2.21)	0.42 (0.01-4.73)

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; Fer, ferritin; FIB, fibrinogen; GGT, gamma glutamyl-transferase; Hb, haemoglobin; Hct, haematocrit; IGs, immature granulocytes; LDH, lactate dehydrogenase; Lym, lymphocytes; NLR, neutrophil-to-lymphocyte ratio; Neu, neutrophils; PLTs, platelets; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell.

respiratory syndrome, with a COVID-19 mortality rate of up to 60% (27,28).

Biomarkers such as NLR, CAR and albumin have all been reported as predictors of poor outcomes in patients with COVID-19 (29-31). To the best of our knowledge, the present study is the first to demonstrate the association of these specific inflammatory biomarkers with unfavourable outcomes among elderly patients receiving early remdesivir treatment, indicating the critical role of the nutritional and inflammatory state of these patients in the course of the disease.

The present study has some limitations which should be mentioned. The major limitation is the lack of a control group due to the prospective observational design and ethical issues. Secondly, this was a single-centre study. Thirdly, during the follow-up period, only a few events occurred that did not permit the performance of multivariable analysis in order to define independent factors associated with poor outcomes.

In conclusion, the safety and efficacy of prophylactic administration of a 3-day regimen of remdesivir for the prevention of severe COVID-19 disease in elderly patients are high. NLR, CAR ratio, albumin value and the presence of hematological malignancy are associated with poor outcomes.

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Availability of data and materials

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

Authors' contributions

NVS and VEG conceptualized the study. VEG, AG, DB, DAS, SM, AT, GK, MNG, PMV, EM, CVP and NVS made

substantial contributions to data interpretation and analysis, and wrote and prepared the draft of the manuscript. VEG and NVS analysed the data and provided critical revisions. VEG and NVS confirm the authenticity of all the data. All authors contributed to manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in line with the Declaration of Helsinki and obtained approval from the regional Institutional Review Board (approval no. 765/12-2021). Written informed consent was obtained from all the included patients.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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