
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Radiology 165 (2023) 110892

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

# Embolization of active arterial bleeding in COVID-19 patients: A multicenter study

Hannah L. Steinberg [a,1,*], Timo A. Auer [b,c,1], Bernhard Gebauer [b], Roman Kloeckner [d], Malte Sieren [d], Peter Minko [e], Kai Jannusch [e], Moritz Wildgruber [f], Vanessa F. Schmidt [f], Daniel Pinto dos Santos [g,h], Thomas Dratsch [g], Jan B. Hinrichs [i], Giovanni Torsello [j], Fabian Stoehr [k], Lukas Müller [k], Frank Herbstreit [l], Michael Forsting [a], Benedikt M. Schaarschmidt [a]

[a] Institut für Diagnostische und Interventionelle Radiologie, Universitätsmedizin Essen, Germany
[b] Klinik für Radiologie, Charité Universitätsmedizin Berlin, Germany
[c] Berlin Institute of Health (BIH), Anna-Louisa-Karsch-Straße 2, 10178 Berlin, Germany
[d] Institut für Interventionelle Radiologie, Universitätsklinikum Schleswig-Holstein, Germany
[e] Institut für Diagnostische und Interventionelle Radiologie, Universitätsklinikum Düsseldorf, Germany
[f] Klinik und Poliklinik für Radiologie, LMU Klinikum München, Germany
[g] Institut für Diagnostische und Interventionelle Radiologie, Universitätsklinikum Köln, Germany
[h] Institut für Diagnostische und Interventionelle Radiologie, Universitätsklinikum Frankfurt, Germany
[i] Institut für Diagnostische und Interventionelle Radiologie, Medizinische Hochschule Hannover, Germany
[j] Institut für Diagnostische und Interventionelle Radiologie, Universitätsmedizin Göttingen, Germany
[k] Klinik und Poliklinik für Diagnostische und Interventionelle Radiologie, Universitätsmedizin Mainz, Germany
[l] Klinik für Anästhesiologie und Intensivmedizin, Universitätsmedizin Essen, Germany

ARTICLE INFO

*Keywords:*
Angiography
COVID 19
Hemorrhage

ABSTRACT

*Purpose:* The purpose of this study was to assess the efficacy of transarterial embolization in COVID-19 patients with an arterial bleeding and to investigate differences between various patient groups concerning survival.
*Method:* We retrospectively reviewed COVID-19 patients undergoing transarterial embolization due to an arterial bleeding in a multicenter study from April 2020 to July 2022 and analyzed the technical success of embolization and survival rate. 30-day survival between various patient groups was analyzed. The Chi- square test and Fisher's exact test were used for testing association between the categorical variables.
*Results:* 53 COVID-19 patients (age: 57.3 ± 14.3 years, 37 male) received 66 angiographies due to an arterial bleeding. The initial embolization was technically successful in 98.1% (52/53). In 20.8% (11/53) of patients, additional embolization was necessary due to a new arterial bleeding. A majority of 58.5% (31/53) had a severe course of COVID-19 infection necessitating ECMO-therapy and 86.8% (46/53) of patients received anticoagulation. 30-day survival rate in patients with ECMO-therapy was significantly lower than without ECMO-therapy (45.2% vs. 86.4%, $p = 0.004$). Patients with anticoagulation did not have a lower 30-day survival rate than without anticoagulation (58.7% vs. 85.7%, $p = 0.23$). COVID-19 patients with ECMO-therapy developed more frequently a re-bleeding after embolization than non-ECMO-patients (32.3% vs. 4.5%, $p = 0.02$).
*Conclusions:* Transarterial embolization is a feasible, safe, and effective procedure in COVID-19 patients with arterial bleeding. ECMO-patients have a lower 30-day survival rate than non-ECMO-patients and have an increased risk for re-bleeding. Treatment with anticoagulation could not be identified as a risk factor for higher mortality.

* Corresponding author at: Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany.
*E-mail address:* Hannah.Steinberg@uk-essen.de (H.L. Steinberg).
[1] Both authors contributed equally to this study.

https://doi.org/10.1016/j.ejrad.2023.110892
Received 7 April 2023; Received in revised form 6 May 2023; Accepted 23 May 2023
Available online 26 May 2023
0720-048X/

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease caused by the severe acute respiratory distress coronavirus 2 (SARS-CoV-2) firstly detected in Wuhan, China, in December 2019 [1]. Although the majority of patients experience a rather mild illness with cough and fever, up to 5% develop severe clinical symptoms with respiratory failure, shock, or multiorgan dysfunction [2]. In patients with severe acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) is the sole therapeutic option necessitating anticoagulation to prevent thrombosis and potential lethal device failure [3].

Due to a frequent underlying coagulopathy, anticoagulation therapy is a delicate balancing act in COVID-19 patients. Especially at the beginning of the pandemic, deep vein thrombosis, pulmonary embolism, and arterial thrombosis were frequently observed in COVID-19 patients [4,5]. Hence, the increased risk of thromboembolic events associated with SARS-CoV-2 [6,7] and the additional benefit of early anticoagulation [8] was debated extensively in the literature. A possible mechanism might be either endothelial dysfunction where an increased release of Angiotensin 2-converting enzyme (ACE2) by epithelial cells leads to reduced levels of angiotensin I which acts as a vasodilator and probably causing direct damage or a strong inflammatory response leading to the so called “cytokine storm” imbalancing platelet production and disruption [9–11]. Besides the well-known risk factors associated with hospitalization such as immobilization, mechanical ventilation, and ICU treatment, COVID-19 induced coagulopathy plays a crucial role in development of thromboembolic events [4,9,12].

The increased bleeding risks in COVID-19 patients aroused less attention [13]. Still, disseminated intravascular coagulation is frequently found in deceased COVID-19 patients [9]. In the literature, bleeding rates of 3.5–8% have been reported in COVID-19 patients, more often in elderly, male, and critically ill patients [14,15]. The majority of bleedings were observed in the gastrointestinal tract, bronchopulmonary system, intracranial and in the soft tissue [16,17]. These bleedings are of considerate interest, as recent studies found an association between an increased bleeding rate and a higher mortality in COVID-19 patients [18,19].

Although the complex interplay of COVID-19 infections and coagulations is still under investigation, active bleeding remains an important complication in the treatment of COVID-19 patients. As surgical management is associated with a considerate mortality and conservative management might not be sufficient due to the underlying coagulative disorder, transarterial embolization has been advocated as a swift and minimally invasive treatment option in these cases [10,20]. However, the reported case number is still too low to derive general recommendations. Therefore, the aim of the present study was to assess the safety and outcome of transarterial embolization of arterial bleedings in COVID-19 infected patients and to investigate differences between various patient groups concerning survival.

## 2. Materials and methods

For this retrospective study, data from nine university hospitals in Germany were collected. COVID-19 patients ≤18 years with arterial bleeding referred to the radiological department that underwent a diagnostic angiography for interventional treatment were included. COVID-19 had to be confirmed either by an antigen test or polymerase chain reaction with a nasal and/or oropharyngeal swab Exclusion criteria were a patient age of less than 18 years, the termination of the procedure prior to the acquisition of angiographic images, missing clinical or radiological records and the lack of a positive COVID-19 test. Datasets from nine tertiary care hospitals in Germany from April 2020 to July 2022 were analyzed. All required data were obtained from the clinical, radiological, and laboratory reports. Ethical approval was confirmed by the respective ethic committees of the participating centers, which was in accordance to the Declaration of Helsinki. The requirement to obtain informed consent was waived due to the retrospective nature of this study (approval number: 22-10857-BO, approval date: 02.08.2022).

### 2.1. Bleeding diagnostics and treatment

By default, patients with clinical suspicion of active bleeding underwent CT imaging of the chest and/or abdomen with intravenous

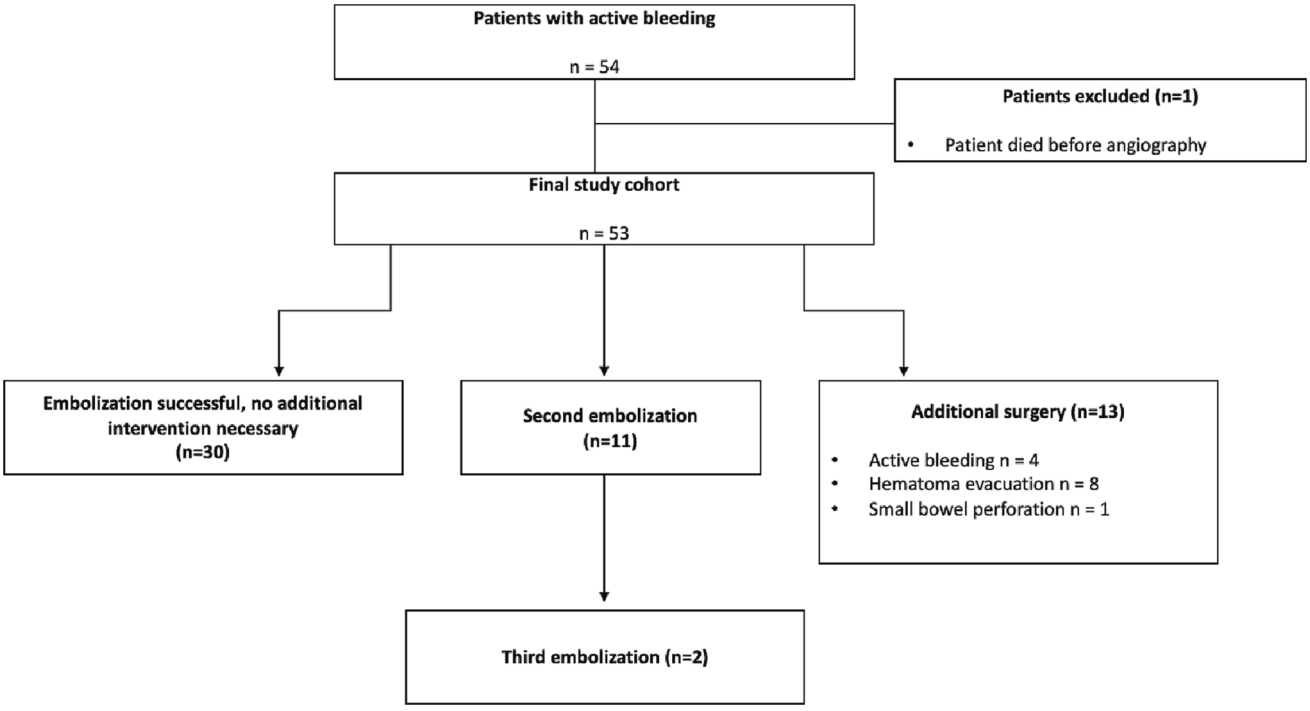


**Fig. 1.** Flowchart of the study cohort.

**Table 1**
Baseline characteristics of the study cohort.

| Demographics | | All patients (n = 53) | Patients with ECMO (n = 31) | Patients without ECMO (n = 22) | P value | Patients with Anticoagulation (n = 46) | Patients without Anticoagulation (n = 7) | P value |
|---|---|---|---|---|---|---|---|---|
| | Age (years) | 57.3 ± 14.3 | 56.7 ± 9.3 | 58.1 ± 19.5 | 0.74 | 59 ± 12.9 | 46.3 ± 19.2 | 0.03 |
| | Sex | 30.2% (16/53) female | 29% (9/31) female | 31.8% (7/22) female | 1 | 30.4% (14/46) female | 28.6% (2/7) female | 1 |
| | Height (cm) | 173.8 ± 10.5 | 174.5 ± 9.5 | 172.7 ± 12.2 | 0.58 | 172.6 ± 10.1 | 180 ± 10.8 | 0.04 |
| | Weight (kg) | 85.1 ± 20.5 | 87.2 ± 22.4 | 81.5 ± 17.1 | 0.35 | 84.6 ± 21.3 | 88 ± 14.7 | 0.7 |
| Comorbidities | | | | | | | | |
| | None | 34% (18/53) | 38.7% (12/31) | 27.3% (6/22) | | 34.8% (16/46) | 28.6% (2/7) | |
| | Yes | 66% (35/53) | 61.3% (19/31) | 72.7% (16/22) | 0.56 | 66.4% (31/46) | 57.1%% (4/7) | 1 |
| | Diabetes | 30.2% (16/53) | 29% (9/31) | 31.8% (7/22) | | 32.6% (15/46) | 28.6% (2/7) | |
| | Hypertension | 49.1% (26/53) | 48.4% (15/31) | 50% (11/22) | | 50% (23/46) | 42.9% (3/7) | |
| | Cardiovascular disease | 35.8% (19/53) | 35.5% (11/31) | 36.4% (8/22) | | 39.1% (18/46) | 14.3% (1/7) | |
| | Kidney disease | 15.1% (8/53) | 9.7% (3/31) | 22.7% (5/22) | | 15.2% (7/46) | 14.3% (1/7) | |
| | Oncological disease | 3.8% (2/53) | 3.2% (1/31) | 4.5% (1/22) | | 2.2% (1/46) | 14.3% (1/7) | |
| | Organ transplantation | 3.8 (2/53) | 0% (0/31) | 9.1% (2/22) | | 4.3% (2/46) | 0% (0/7) | |
| $O^2$ treatment during hospitalization | | | | | | | | |
| | None | 15.1% (8/53) | 0% (0/31) | 36.4% (8/22) | | 8.5% (4/46) | 57.1%% (4/7) | |
| | $O^2$ treatment | 84.9% (45/53) | 100% (31/31) | 63.6% (14/22) | <0.001 | 91.5% (42/46) | 42.9% (3/7) | 0.007 |
| Dialysis | | | | | | | | |
| | Yes | 47.2% (25/53) | 58.1% (18/31) | 31.8% (7/22) | 0.09 | 46.8% (21/46) | 57.1% (4/7) | 1 |
| | No | 52.8% (28/53) | 31.7% (13/31) | 68.2% (15/22) | | 53.2% (25/46) | 42.9% (3/7) | |
| COVID-19 specific medication | | | | | | | | |
| | None | 67.9% (36/53) | 67.7% (21/31) | 68.2% (15/22) | | 68.1% (31/46) | 71.4% (5/7) | |
| | Yes | 32.1% (17/53) | 32.3% (10/31) | 31.8% (7/22) | 0.63 | 31.9% (15/46) | 28.6% (2/7) | 1 |

contrast media and at least an arterial and venous phase in a multi-detector CT to confirm a bleeding and identify its origin. If a bleeding was detected, the therapeutic concept was discussed between the responsible physician, surgeons, and an interventional radiologist. Patients considered as eligible for embolization were transferred to the angiographic suite for treatment. In exceptional cases, the patients were transferred to the angiography suite without prior CT diagnostics because the bleeding location was already known, and further diagnostics and treatment was performed.

Femoral or radial access was used for sheath insertion. Through a guiding catheter, a microcatheter was navigated to the previously identified vascular territory and angiography was performed. The target vessel was catheterized selectively for embolization. The choice of the embolizing agent depended on the interventional radiologists' preferences and experience as well as the on the patient's anatomy and the position of the bleeding site. Here, either glue (e.g. Histoacryl, B. Braun, Melsungen, Germany; Glubran, GEM Srl, Viareggio, Italy; Onyx Liquid Embolic System, Medtronic, Dublin, Ireland), particles (uncalibrated particles e.g. Contour PVA Embolization particles, Boston Scientific, Marlborough, UAS, or calibrated particles e.g. Embozene Microspheres, Boston Scientific, Marlborough, USA), micro coils (e.g. IDC Detachable Embolization Coils, Boston Scientific, Marlborough, USA; Hilal Embolization Cook Coils, COOK Medical, Bloomington, USA), gelantine sponge, or a mixture of the previously mentioned materials was used. At the end of the intervention, the puncture site was closed either by a vascular closure device (Angioseal, Terumo Corporation, Japan or Perclose ProGlide, Abbott Vascular, Redwood City, USA) or by manual compression.

### 2.2. Statistics

Continuous variables are presented as mean with standard deviation in case of normal distribution or as median with range. Categorical variables are presented as count. The Chi-square test and Fisher's exact test were used for testing association between categorical and the Mann-Whitney-*U* test or *t*-test for continuous variables. To assess the influence of ECMO-treatment, anticoagulation, intensive care unit (ICU) treatment, COVID-19 specific medication, comorbidities, and the need for additional treatment on survival, a comparison between the different subgroups was compared concerning the 14-day and 30-day survival rate. Additionally, Kaplan Meyer curves were used to assess the impact of ECMO-treatment and anticoagulation on survival and analyzed using the log-rank test. $p < 0.05$ was considered as statistically significant. Because of the exploratory nature of this study, no correction for ɑ-error accumulation was performed. All statistical analyses were carried out with SPSS 28.0 (IBM, Chicago, USA) and R4.2.0 (R Core Team, 2022).

## 3. Results

### 3.1. Patients' characteristics

The initial dataset consisted of 54 patients. One patient died in the angiography suite prior to any kind of invasive maneuver and was therefore excluded from further analysis. Hence, this retrospective study included 53 patients (16 female, 37 male), aged from 23 to 90 years (mean 57.7 ± 14.3 years) from nine different university hospitals in Germany (Fig. 1). In 15.1% (8/53), patients experienced a mild course of

**Table 2**
Site of active arterial bleeding in COVID-19 patients.

| Site of bleeding | Interventions (n = 66) |
|---|---|
| Thoracic wall | 27.3% (18/66) |
| Head and neck | 12.1% (8/66) |
| Bronchopulmonary system | 10.6% (7/66) |
| Lumbar artery | 9.1% (6/66) |
| Gastrointestinal tract | 9.1% (6/66) |
| Inguinal region | 6.1% (4/66) |
| Abdominal wall | 6.1% (4/66) |
| Pelvis | 6.1% (4/66) |
| Gynecological tract | 4.5% (3/66) |
| Retroperitoneum | 3% (2/66) |
| Liver | 3% (2/66) |
| Splenic artery | 1.5% (1/66) |
| Kidney | 1.5% (1/66) |

the disease with symptoms such as cough and/or fever without the need for oxygen treatment during hospitalization. In 84.9% (45/53), a more severe course was observed and oxygen treatment (e.g. via nasal cannula, high flow ventilation, mechanical ventilation) was necessary. In total, 90.6% (48/53) of patients required ICU treatment and 58.5% (31/53) necessitated ECMO-therapy. 86.8% (46/53) of patients received anticoagulation therapy. Except for one patient (3.2% (1/31)) who did not receive anticoagulation as an individual therapy concept due to a spontaneous prolonged activated clotting time, all other ECMO-patients received anticoagulation (96.8% (30/31)). On average, embolization was performed 19 ± 16.7 days after admission (see Table 1 for further patient characteristics).

### 3.2. Bleeding diagnostics and treatment

In total, 66 endovascular interventions were performed in 53 patients. In 20.8% (11/53) of patients, a second embolization was necessary after initial embolization. On average, the additional intervention was performed 7.1 ± 11 days after the initial procedure. A third embolization was necessary in selected cases (3.8%, 2/53). In the majority of cases, re embolization was performed at the same location in 76.9% (10/13). Before the angiography, in 95.5% (63/66) of cases a CT scan was performed, 4.5% (3/66) were directly transferred to the angiographic suite. The bleeding site was most often localized in the thoracic wall in 27.3% (18/66), head and neck in 12.1% (8/66), followed by the bronchopulmonary system in 10.6% (7/66), the lumbar

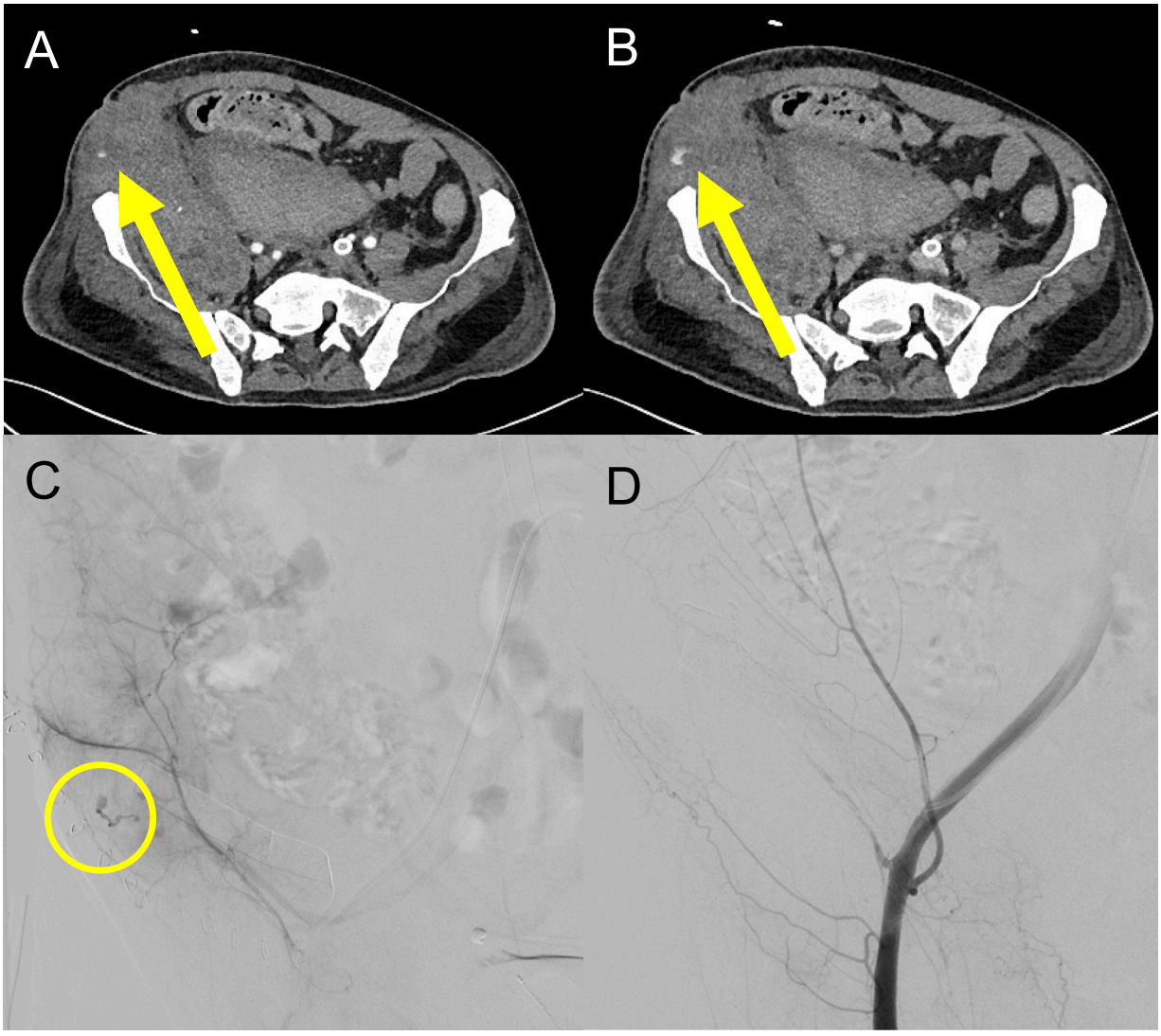


**Fig. 2.** A 66-year-old male patient with COVID-19 infection necessitating ECMO treatment developed a multifocal, active arterial bleeding from the right deep circumflex iliac artery with a large hematoma in the CT in the arterial (A) und porto-venous phase (B). (C) In the angiography, extravasation of contrast media from the deep circumflex iliac artery could be seen and endovascular treatment was performed. The deep circumflex iliac artery was occluded with coils and glue to stop the bleeding. (D) In the control series, no extravasation of contrast media could be detected.

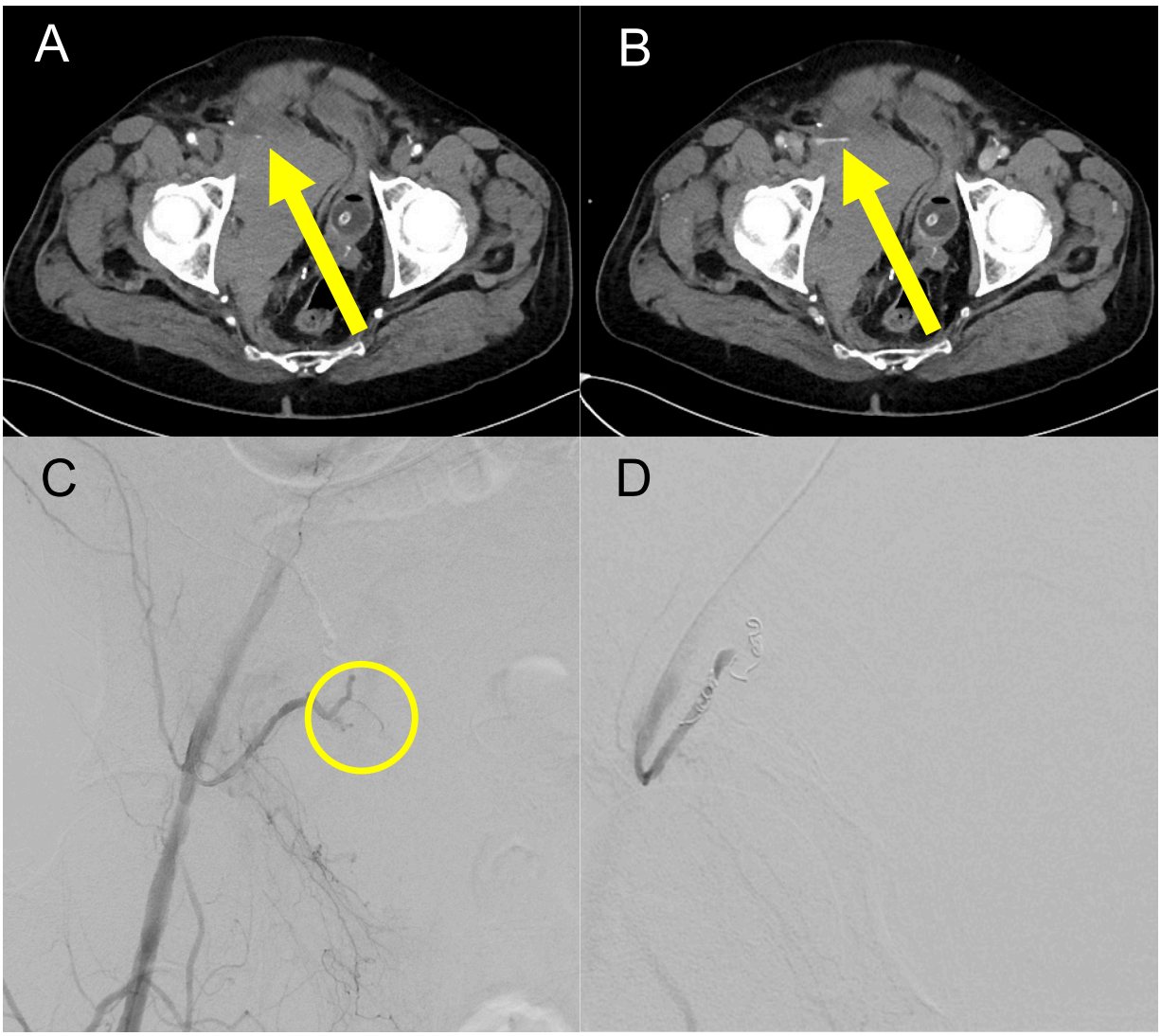


**Fig. 3.** A 60-year-old male patient with COVID-19 infection without ECMO or anticoagulation treatment developed an active arterial bleeding from the inferior gastric artery with a large hematoma in the CT in the arterial (A) und porto-venous phase (B). (C) In the angiography, extravasation of contrast media from the inferior gastric artery could be seen and endovascular treatment was performed. The inferior gastric was occluded with coils gelantine sponge to stop the bleeding. (D) In the control series, no extravasation of contrast media could be detected.

arteries and the gastrointestinal tract in 9.1% (6/66), respectively. The bleeding was localized in 6.1% (4/66) either in the pelvis, the inguinal region or in the abdominal wall and in 4.5% (3/66) in the gynecological tract. Less frequently, bleeding was found in the retroperitoneum or in the liver (3% (2/66), respectively), or arising from the splenic artery or the kidney (1.5% (1/66), respectively, see Table 2). Spontaneous bleeding was observed in 69.7% (46/66). Iatrogenic bleeding occurred in 30.3% (20/66), most frequently after chest tube placement in 50% (10/20), placement of central venous catheters in 25% (5/20), and in 5% (1/20) after ECMO cannulation, kidney biopsy, trauma, TIPPS, and reanimation, respectively.

In all 66 interventions, a transfemoral access was used. An additional transradial access was necessary in one patient for additional stent implantation to stop the bleeding. Various embolic agents were used: glue 31.8% (21/66), micro coils 51.5% (34/66), particles 51.5% (34/66), and a gelatin sponge in 10.6% (7/66). A mixture of the above-mentioned products was used in 69.7% (46/66). In 98.1% (52/53) of patients, the embolization was technically successful, and the patients could be transferred to the ward afterwards (Figs. 2, 3, 4). One patient died in the angiographic suite from a cardiogenic shock (1.9% (1/53)). In 24.5% (13/53) of patients, additional surgery was needed. However, only in 7.5% (4/53) of patients, surgery was necessary to control the bleeding. In the other cases, surgery was necessary for hematoma evacuation in 15.1% (8/53) and because of small bowel perforation in 1.9% (1/53). Additional re-embolization was significantly more frequent in ECMO-patients than in non-ECMO-patients (32.3% (10/31) vs. 4.5% (1/22), $p = 0.02$).

### 3.3. Survival analysis

A total of 52.8% (28/53) of patients were alive at the cutoff date of the analysis (01.09.2022). The average time to discharge was 38 ± 49 days after the initial intervention. 47.2% (25/53) of patients died. The average timepoint of death was 12 ± 25 days after the intervention. The causes of death were either multiorgan failure in 44% (11/25), different types of shock (hemorrhagic, septic, or cardiogenic) in 32% (8/25), or respiratory insufficiency in 12% (3/25). In 12% (3/25) of patients, the causes of death was unclear. In the entire study population, 14-day survival rate was 75.5% (40/53) and 30-day survival rate was 67.9% (36/53) after the initial procedure.

In ECMO-patients, 14-day survival rate was 67.7% (21/31) and 30-day survival rate was 45.2% (14/31). According to Fisher's exact test,

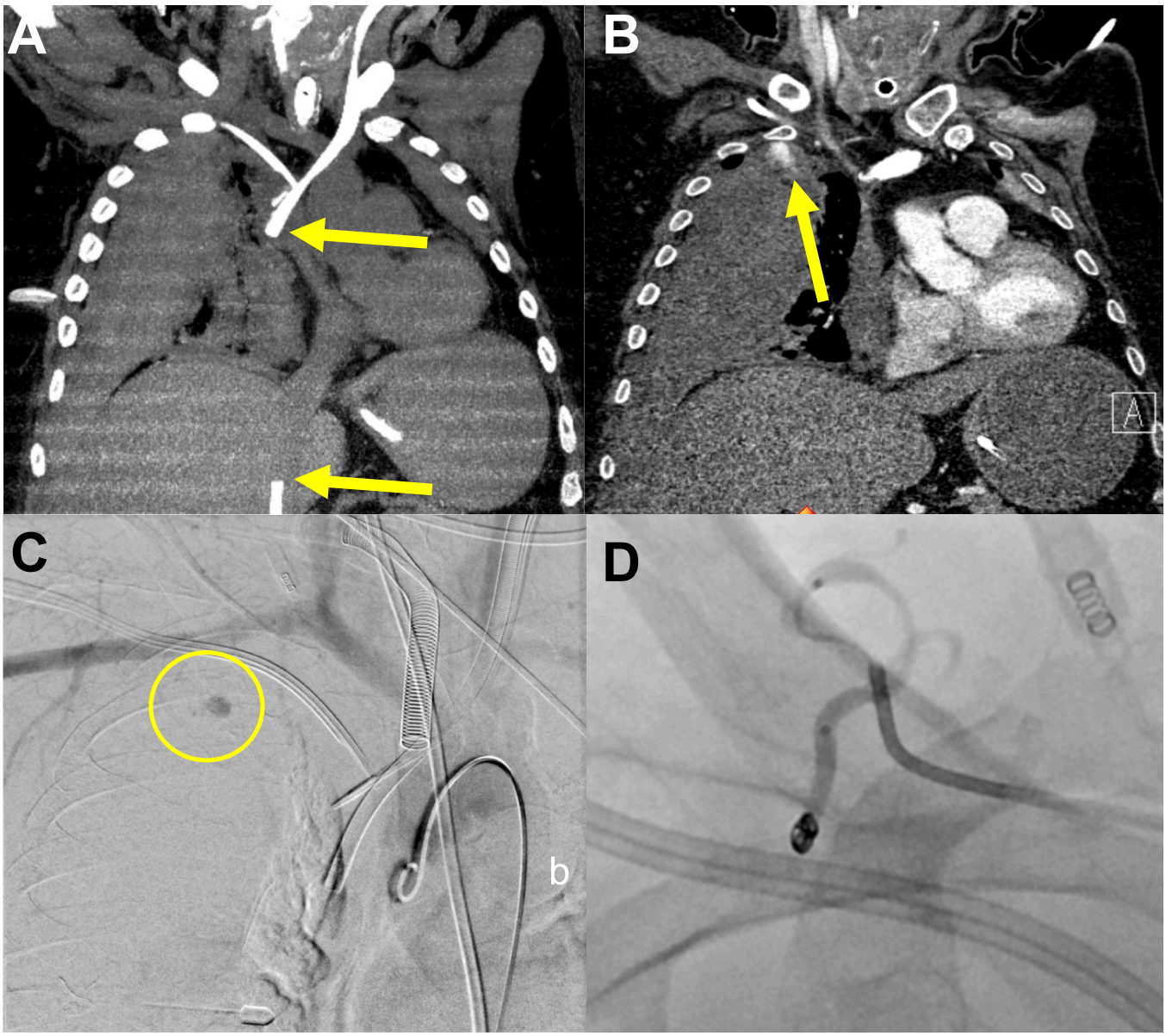


**Fig. 4.** A 59-year-old male patient with a COVID-19 induced ARDS necessitating venous-venous-ECMO treatment (yellow arrow pointing at the cannulas in A, non-contrast enhanced CT) developed a spontaneous active arterial bleeding and large thoracic hematoma probably originating from a subclavian artery side branch (yellow arrow in B, contrast enhanced CT). After access via the right groin, the bleeding was confirmed via aortography and an origin from of a lateral branch of the thyrocervical trunk was identified as a bleeding source (C, yellow circle). By selective probing of the mentioned branch with a microwire and catheter, the catheter was advanced to the bleeding source. Combined particle and coil embolization was performed until stasis in the target vessel was reached (D).

no significant differences were observed for the 14-day survival rate (ECMO-patients 67.7%, non-ECMO-patients 90.1%; $p = 0.09$). However, the 30-day survival rate (ECMO-patients 45.2%, non-ECMO-patients 86.4%; $p = 0.004$) was significantly lower in ECMO-patients compared to the rest of the analyzed cohort. According to the log rank test, survival was significantly longer in non-ECMO than in ECMO-patients ($\chi^2 = 3.9897$, $p = 0.046$, Fig. 5A).

If patients receiving anticoagulation therapy, 14-day survival rate was 76% (35/46) and 30-day survival rate was 58.7% (27/46) after the initial intervention. No statistically significant differences between patients with or without anticoagulation were observed regarding the 14-day survival rate (anticoagulation 76%, no anticoagulation 85.7%; $p = 0.68$), the 30-day survival rate (anticoagulation 58.7%, no anticoagulation 85.7%; $p = 0.23$) and the log rank test ($\chi^2 = 0.038732$, $p = 0.0844$, Fig. 5B).

In patients with and without the need for ICU treatment, similar 14-day (ICU treatment 74.4%, no ICU treatment 100%, $p = 0.32$) and 30-day survival rates (ICU treatment 57.4%, no ICU treatment 100%, $p = 0.07$) were found according to Fisher's exact test. No significant differences concerning the two survival rates were observed concerning the presence of comorbidities (14-day survival: with comorbidities 71.4%, no comorbidities 88.9%, $p = 0.19$; 30-day survival: with comorbidities 62.9%, no comorbidities 61.1%, $p = 1$) as well as COVID-19 specific treatment (14-day survival: with COVID-19 specific treatment 64.7%, no COVID-19 specific treatment 83.3%, $p = 0.17$; 30-day survival: with COVID-19 specific treatment 52.9%, no COVID-19 specific treatment 66.7%, $p = 0.38$) according to the Fisher's exact test.

There was no statistically significant difference in 14-day und 30-day survival if a second treatment (e.g. embolization or surgery) was necessary according to Fisher's exact test (14-day survival rate: additional therapy (e.g. embolization or surgery) needed: 88.9%, no additional therapy needed 68.6%, $p = 0.18$; 30-day survival rate: additional

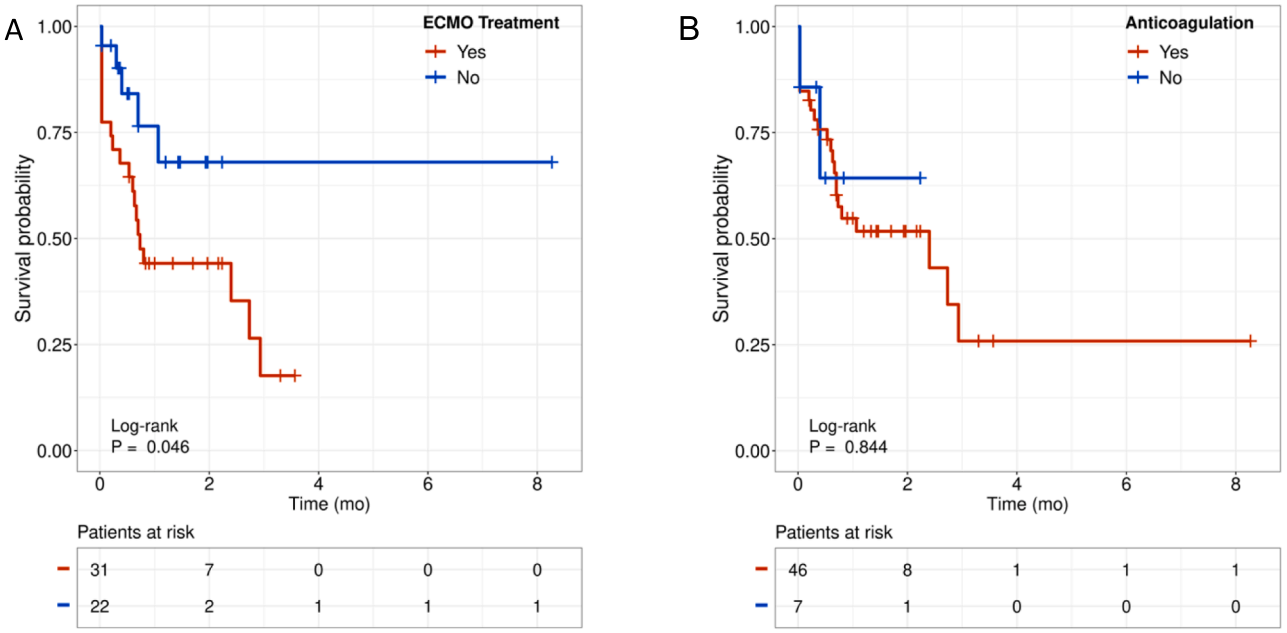


**Fig. 5.** Kaplan-Meyer analysis of survival in COVID-19 patients with arterial bleeding undergoing transarterial embolization (A: ECMO-therapy B: anticoagulation).

therapy needed 72.2%, no additional therapy needed 57.1%, p = 0.37; see Table 1).

## 4. Discussion

In the present study, we aimed to assess the safety and outcome of transarterial embolization of bleedings in COVID-19 patients. The pooled data from nine tertiary care centers yielded two major findings. First, we could show that COVID-19 patients with ECMO-therapy necessitating embolization had lower survival rate after transarterial treatment compared to non-ECMO-patients. Additionally, repeated embolizations were significantly more frequent in ECMO-patients than in non-ECMO-patients. Anticoagulation therapy, however, did not seem to have a significant impact on survival rates or the need for repeated treatment in COVID-19 patients undergoing transarterial embolization.

COVID-19 induced coagulopathy does not only increase the risk of thromboembolic events, but also for the development of major bleedings [14]. This major complication is discussed less in the current literature and its multifactorial etiology is, to date, not fully understood [9]. COVID-19 induced coagulopathy does not only increase the risk of thromboembolic events, but also for the development of major bleedings [14]. In addition, despite the positive effects of anticoagulation therapy associated with the reduced occurrence of thromboembolic events, the negative side effects of this therapy increase the risk for arterial bleedings [18]. Therefore, the dosage of anticoagulation is key to minimize the risk of major bleedings and to ensure patient safety [10,14]. Anticoagulation treatment was administered in 86.8% of patients in our study. However, a significant impact on survival rates was not observed here. Additionally, we did not find significant differences in the need for repeated transarterial embolizations between patients with and without anticoagulation therapy. Still, it remains difficult to identify risk factors leading to major bleedings, and consequently, to a potentially worse outcome in a multimorbid patient group. Consecutively, the prevention of bleedings is of special interest in patients necessitating ICU treatment or even ECMO-therapy, which is known to be associated with increased bleeding risk [12].

ECMO therapy is associated with a high mortality ranging from 45% to 55.6% [3,21]. Even before the COVID-19 pandemic, major bleeding was a relevant problem in ECMO-patients. The incidence of major bleedings was described with 39.4% in patients with venous-venous and with 51% in patients with veno-arterial ECMO [22].

In COVID-19 patients with respiratory failure, ECMO-therapy is a frequent rescue therapy and is associated with a survival rate between 51% and 62.9% [23,24]. COVID-19 patients necessitating ECMO-therapy have higher mortality rates compared to non-COVID-19 patients which is well documented in the literature [23]. This increased mortality rate is not only attributable to ECMO-associated thrombosis, but also to bleeding events (e.g. caused by the need for anticoagulation, thrombozytopenia, hypofibrinogenemia etc). Here, the probability of bleeding events is associated to the duration of ECMO treatment [25,26]. The results of our study demonstrate the significant negative impact of ECMO treatment on survival, which can be also observed in patients requiring transarterial embolization. However, these results must be interpreted with caution. In multimorbid patients, it is difficult to identify an isolated cause of death. As ECMO treatment is only performed in patients with severe COVID-19 infections, it is highly possible that the cause of death could not only be attributed to the bleeding, but to other factors caused by the infection as well. Hence, ECMO treatment could be considered an important confounder in the present scenario. Another indicator for this interpretation is the fact that we observed a significant increase in the need for repeated embolizations in ECMO-patients compared to non-ECMO-patients. However, patients necessitating repeated interventions did not show lower survival rates. As the success rate was very high in the present analysis, transarterial embolization should be considered the method of choice to treat bleedings in COVID-19 patients, if technically feasible. As a variety of embolic agents was used in most cases, these interventions have to be considered as challenging, underlining the need to treat severely ill COVID-19 patients in tertiary care centers.

In addition to COVID-19 induced coagulopathy, there are several factors which have an effect on the severity of the disease and the mortality rate [27]. Studies show that especially older patients, patients with comorbidities, and critically ill patients needing ICU treatment have a higher mortality rate [27–29]. Furthermore, the literature describes the presence of chronic renal failure or the development of acute renal failure with dialysis as a factor associated with increased mortality

[30,31]. However, this factor could not be identified as a risk factor in critically ill patients [32], which represent the majority in our study population. Furthermore, neither comorbidities, nor dialysis could be identified as a risk factor with a lower survival rate. Therefore, ECMO-therapy might be the most important confounder associated with the illness severity in COVID-19 patients. Further analyses might be necessary to specify further predictive factors.

Our study has some limitations. Due to the retrospective and multicenter design, differences in patient selection, interventional technique, and the interventionalists' experience level might have a potential impact on the treatment results. Additionally, our conclusions are limited by the missing control groups receiving either sole conservative or surgical treatment, as well as control group consisting of non-infectious patients. However, the severity of the disease requires a maximum treatment effort, thus, reducing the clinical and ethical practicability of these study designs. A further limitation of the presented study is the difficulty to assess the cause of death as well as the cause of bleeding in a retrospective study design. In patients with iatrogenic bleedings, for example, it is impossible to decide whether the bleeding was caused by the procedure alone or occurred due to COVID-19 associated coagulopathy after an intervention, which would have been tolerated in patients without COVID-19 infection. Therefore, this differentiation was not made in the present analysis.

Our results shows that transarterial embolization is a feasible, safe, and effective procedure for treatment for active arterial bleeding in COVID-19 patients. Critically ill patients necessitating ECMO-therapy have a lower 30-day survival rate than non-ECMO-patients and have a higher risk to develop re-bleeding needing additional interventions. Anticoagulation could not be identified as a risk factor for survival.

**Funding:**

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

## CRediT authorship contribution statement

**Hannah L. Steinberg:** Conceptualization, Methodology, Data curation, Writing – Original Draft, Formal Analysis, Visualization, Project administration. **Timo A. Auer:** Conceptualization, Methodology, Writing – Original Draft, Visualization, Project administration. **Bernhard Gebauer:** Resources, Writing – Review & Editing. **Roman Kloeckner:** Resources, Writing – Review & Editing. **Malte Sieren:** Resources, Writing – Review & Editing. **Peter Minko:** Resources, Writing – Review & Editing. **Kai Jannusch:** Resources, Writing – Review & Editing. **Moritz Wildgruber:** Resources, Writing – Review & Editing. **Vanessa F. Schmidt:** Resources, Writing – Review & Editing. **Daniel Pinto dos Santos:** Resources, Writing – Review & Editing. **Thomas Dratsch:** Resources, Writing – Review & Editing. **Jan B. Hinrichs:** Resources, Writing – Review & Editing. **Giovanni Torsello:** Resources, Writing – Review & Editing. **Fabian Stoehr:** Resources, Writing – Review & Editing. **Lukas Müller:** Resources, Writing – Review & Editing. **Frank Herbstreit:** Investigation, Writing – Review & Editing. **Michael Forsting:** Writing – Review & Editing. **Benedikt M. Schaarschmidt:** Conceptualization, Methodology, Writing – Review & Editing, 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] W.J. Wiersinga, A. Rhodes, A.C. Cheng, S.J. Peacock, H.C. Prescott, Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review, JAMA 324 (2020) 782–793.
[2] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the chinese center for disease control and prevention, JAMA 323 (2020) 1239–1242.
[3] B. Friedrichson, H. Mutlak, K. Zacharowski, F. Piekarski, Insight into ECMO, mortality and ARDS: a nationwide analysis of 45,647 ECMO runs, Critical Care 25 (2021) 38.
[4] B. Bikdeli, M.V. Madhavan, D. Jimenez, et al., COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-Up: JACC state-of-the-art review, J. Am. Coll. Cardiol. 75 (2020) 2950–2973.
[5] M. Marietta, W. Ageno, A. Artoni, et al., COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET), Blood Transfus. 18 (2020) 167–169.
[6] F. Klok, M. Kruip, N. Van der Meer, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147.
[7] T. Wang, R. Chen, C. Liu, et al., Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19, Lancet Haematol. 7 (2020) e362–e363.
[8] A. Kollias, K.G. Kyriakoulis, E. Dimakakos, G. Poulakou, G.S. Stergiou, K. Syrigos, Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action, Br. J. Haematol. 189 (2020) 846–847.
[9] C. Tudoran, D.E. Velimirovici, D.M. Berceanu-Vaduva, M. Rada, F. Voiţă-Mekeres, M. Tudoran, Increased susceptibility for thromboembolic events versus high bleeding risk associated with COVID-19, Microorganisms 10 (2022).
[10] A.M. Ierardi, A. Coppola, S. Tortora, et al., Gastrointestinal bleeding in patients with SARS-CoV-2 infection managed by interventional radiology, J. Clin. Med. 10 (2021).
[11] N.C. Chan, J.I. Weitz, COVID-19 coagulopathy, thrombosis, and bleeding, Blood 136 (2020) 381–383.
[12] Y. Wang, L. Shi, H. Yang, G. Duan, Y. Wang, Pooled prevalence of deep vein thrombosis among coronavirus disease 2019 patients, Crit. Care 24 (2020) 466.
[13] B.M. Schaarschmidt, D. Fistera, Y. Li et al., Streamlining patient management of suspected COVID-19 patients in the emergency department: incorporation of pulmonary CT angiography into the triaging algorithm. Diagnostics (Basel) 12 (2022).
[14] H. Al-Samkari, R.S. Karp Leaf, W.H. Dzik, et al., COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection, Blood 136 (2020) 489–500.
[15] A. Shah, K. Donovan, A. McHugh, et al., Thrombotic and haemorrhagic complications in critically ill patients with COVID-19: a multicentre observational study, Crit. Care 24 (2020) 561.
[16] S. Zellmer, F. Hanses, A. Muzalyova, et al., Gastrointestinal bleeding and endoscopic findings in critically and non-critically ill patients with corona virus disease 2019 (COVID-19): results from Lean European Open Survey on SARS-CoV-2 (LEOSS) and COKA registries, United European Gastroenterol. J. 9 (2021) 1081–1090.
[17] G.N. Nadkarni, A. Lala, E. Bagiella, et al., Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19, J. Am. College Cardiol. 76 (2020) 1815–1826.
[18] N. Musoke, K.B. Lo, J. Albano, et al., Anticoagulation and bleeding risk in patients with COVID-19, Thromb. Res. 196 (2020) 227–230.
[19] P. Lucatelli, B. Rocco, P.G. Nardis, et al., Bleeding in COVID patients: what we have understood so far, CardioVasc. Intervent. Radiol. 44 (2021) 666–668.
[20] F. Tiralongo, S. Seminatore, S. Di Pietro, et al., Spontaneous retroperitoneal hematoma treated with percutaneous transarterial embolization in COVID-19 era: diagnostic findings and procedural outcome, Tomography 8 (2022) 1228–1240.
[21] R.R. Thiagarajan, R.P. Barbaro, P.T. Rycus, et al., Extracorporeal life support organization registry international report 2016, ASAIO J. 63 (2017).
[22] S.R. Olson, C.R. Murphree, D. Zonies, et al., Thrombosis and bleeding in extracorporeal membrane oxygenation (ECMO) without anticoagulation: a systematic review, Asaio J. 67 (2021) 290–296.
[23] S.B. Dave, R. Rabinowitz, A. Shah, et al., COVID-19 outcomes of venovenous extracorporeal membrane oxygenation for acute respiratory failure vs historical cohort of non-COVID-19 viral infections, Perfusion (2022), https://doi.org/10.1177/02676591221105603:2676591221105603.
[24] K. Ramanathan, K. Shekar, R.R. Ling, et al., Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis, Crit. Care 25 (2021) 1–11.
[25] D.J. Arachchillage, I. Rajakaruna, I. Scott, et al., Impact of major bleeding and thrombosis on 180-day survival in patients with severe COVID-19 supported with veno-venous extracorporeal membrane oxygenation in the United Kingdom: a multicentre observational study, Brit. J. Haematol. 196 (2022) 566–576.
[26] D.J. Cook, L.E. Griffith, S.D. Walter, et al., The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients, Crit. Care 5 (2001) 368.
[27] Z.G. Dessie, T. Zewotir, Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients, BMC Infect. Dis. 21 (2021) 1–28.
[28] X. Li, S. Xu, M. Yu, et al., Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan, J. Allergy Clin. Immunol. 146 (2020) 110–118.
[29] A. Alharthy, W. Aletreby, F. Faqihi, et al., Clinical characteristics and predictors of 28-day mortality in 352 critically Ill patients with COVID-19: a retrospective study, J. Epidemiol. Glob. Health 11 (2021) 98–104.

[30] T. Menon, S.A.Q. Gandhi, W. Tariq, et al., Impact of chronic kidney disease on severity and mortality in COVID-19 patients: a systematic review and meta-analysis, Cureus 13 (2021).
[31] P. Hansrivijit, C. Qian, B. Boonpheng, et al., Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis, J. Investig. Med. 68 (2020) 1261–1270.
[32] T.J. Wilbers, M.V. Koning, Renal replacement therapy in critically ill patients with COVID-19: a retrospective study investigating mortality, renal recovery and filter lifetime, J. Crit. Care 60 (2020) 103–105.