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ORIGINAL ARTICLE

The utility of transarterial embolization and computed tomography for life-threatening spontaneous retroperitoneal hemorrhage

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Abstract

Purpose To assess the safety and efficacy of transarterial embolization (TAE) and to evaluate the utility of contrast-enhanced computed tomography (CE-CT) for life-threatening spontaneous retroperitoneal hemorrhage (SRH).

Methods Nineteen patients underwent TAE following CE-CT for life-threatening SRH. CE-CT and angiographic findings, technical successes, and clinical successes were evaluated. The diagnostic performance of CE-CT for the detection of active bleeding arteries was also assessed by two independent readers.

Results Active extravasation of contrast material was accurately observed in 78.9−84.2% of the patients on CE-CT. Angiograms revealed active extravasation in 37 arteries of 15 patients (78.9%), and 4 patients showed no sign of active bleeding. Sensitivity, positive predictive value, and accuracy rate of CE-CT for the detection of active bleeding vessels was 59.5%, 62.9−71.0% and 55.6−60.0% respectively. The successful embolization of 48 intended arteries was achieved in all the patients, including empirical TAE in four patients. Hemodynamic stabilization was achieved in 17 patients (89.5%) with a significant decrease in transfusion ($p < 0.001$).

Conclusion TAE is a technically safe and clinically effective treatment method for life-threatening SRH. CE-CT has moderate capability for accurate identification of active bleeding arteries. TAE including arteries that potentially distribute anatomic territory of the hematoma is essential.

Keywords Retroperitoneal hemorrhage · Anticoagulation · Computed tomography · Arterial embolization

Introduction

Spontaneous retroperitoneal hemorrhage (SRH) is defined as a hemorrhaging that occurs beyond the peritoneum without any preceding trauma or underlying pathology [1, 2]. It is a lethal clinical entity with an incidence of 0.6–6.6% that occasionally develops as a complication of anticoagulation therapy, coagulopathy, or hemodialysis [3, 4]. According to the pathogenesis, SRH begins with diffuse occult vasculopathy and arteriosclerosis of mircovessels, which causes larger vessels to become stretched and disrupted as hematoma enlarges [4–6].

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The survival rate of the patients with SRH depends on rapid and accurate diagnoses followed by imperative management, as the bleeding is often insidious and initially unrecognized [4–6]. Computed tomography (CT) is used for the initial diagnosis of retroperitoneal hemorrhage, and the utility of contrast-enhanced CT (CE-CT) to confirm active bleeding vessels in traumatic retroperitoneal hemorrhage has been established [7, 8]. By contrast, the utility of CE-CT for the detection of active bleeding vessels in patients with SRH has not been fully elucidated (Fig. 1).

The management of SRH mainly consisted of conservative treatment [3, 4]. It is difficult to control active hemorrhage through surgical intervention, because the identification and ligation of bleeding vessels are sometimes impossible and open removal of hematoma reduces tamponade effects of the retroperitoneum [5, 9]. Using transarterial embolization (TAE) to treat retroperitoneal hemorrhage caused by trauma or iatrogenic injury is an established

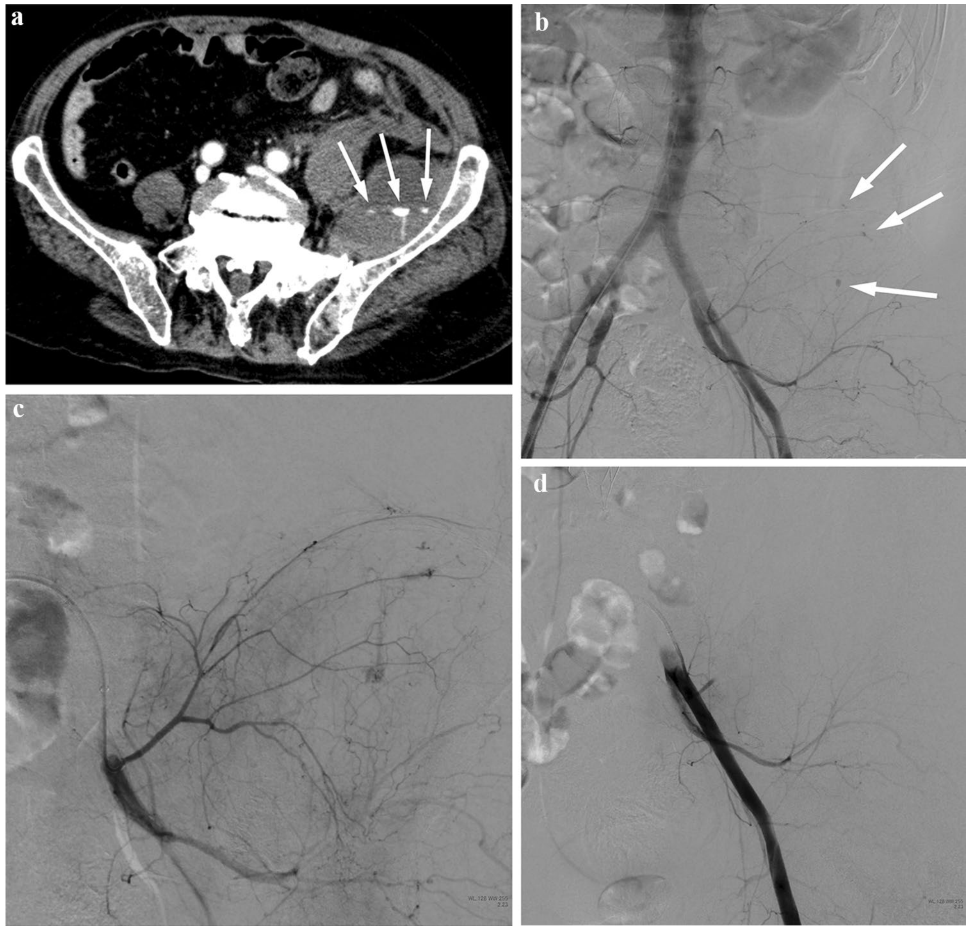

Fig. 1 A 73-year-old male who was anticoagulated for deep venous thrombosis developed spontaneous retroperitoneal hemorrhage. **a** Contrast-enhanced CT image shows retroperitoneal hemorrhage with extravasation of contrast material (arrows). **b** Aortography demonstrates extravasation in the left retroperitoneal territory (arrows). **c** Selective left iliolumbar arteriogram reveals multiple extravasations from muscle branches. d Left iliac arteriogram after embolization with gelatin particle confirms hemostasis with no active bleeding

procedure to preserve tamponade effect [10, 11], but the efficacy for the treatment of SRH has remained unclear due to limited evidence [12–14]. Recently, two studies have reported the utility of TAE but have included patients with extra-retroperitoneal hemorrhage, which included seven and 21 patients in each paper [15, 16]. Therefore, no contemporary consensus exists to suggest when to attempt TAE in the treatment of SRH with a large number of patients.

The purpose of this study was to assess the safety and efficacy of TAE for life-threatening SRH, and to evaluate the utility of CE-CT for the detection of active bleeding vessels.

Materials and methods

Patient population

This retrospective study was approved by our institutional review board with a waiver of informed consent. Between May 2005 and June 2018, 20 consecutive patients underwent TAE following CT for life-threatening SRH. One patient received only unenhanced CT due to impaired renal function. Consequently, 19 patients who underwent TAE following CE-CT were included in this study (Table 1). Seventeen patients were hospitalized, and the remaining two outpatients visited by walk and ambulance. All the patients were initially treated with fluid resuscitation, withdrawal of anticoagulant therapy, and correction treatment for coagulopathy. Sixteen patients were managed in an intensive care unit. In 19 patients, TAE was performed either to treat hemodynamic instability ($n = 14$) and/or progression of anemia despite transfusion ($n = 14$).

Nine patients received cardiovascular interventions before TAE (mean 14.4 days; range 0−44 days). Eighteen of 19 patients received anticoagulant therapy. The one remaining patient with liver cirrhosis suffered from coagulopathy caused by hepatic insufficiency. Five of eighteen patients who had anticoagulant therapy were above the therapeutic range; four patients who received heparin sodium measured an activated partial thromboplastin time (APTT) of more than 100 s, and one patient who received warfarin measured an international normalized ratios (INR) of 4.94. Four patients underwent hemodialysis with use of heparin sodium except for one patient who received gabexate mesilate for anticoagulation. Antiplatelet therapy was taken in seven patients. A variety of subjective symptoms was reported in

Table 1 Patients' characteristics of the study population

Variable	Value
Patient demographics	
Age (year)	
Mean ±SD (range)	69.6 ± 10.7 (46−85)
Median (interquartile range)	73 (64.5−74.5)
Gender	
Male: female	10:09
Underlying disease	
Ischemic heart disease	5
Cardiac valvular disease	3
Aortic aneurysm	3
Rheumatoid arthritis	2
Others	6
Anticoagulant therapy	
Heparin sodium	13
Warfarin	4
Gabexate mesilate	1
Not applicable	1
Antiplatelet therapy	
Aspirin	5
Clopidogrel	1
Aspirin and Clopidogrel	1
Not applicable	12
Clinical characteristics	
Symptoms*	
Abdominal distension	6
Abdominal pain	3
General fatigue	2
Nausea	1
Dyspnea	1
Lumbago	1
Not be evaluated due to conscious sedation	10
Indication for anticoagulant therapy	
Venous thromboembolic disease	9
Rhythmic cardiopathy	4
Acute myocardial infarction	2
Portal vein thrombosis	1
Prophylaxis for deep venous thrombus	1
Hemodialysis	1
Overdosage of anticoagulant therapy**	
Yes:No	05:13
Vasoactive drugs	
Yes:No	13:06
Mechanical ventilation	
Yes:No	06:13
Laboratory data	
Hemoglobin (g/dL)	
Mean ± SD (range)	7.9 ± 2.0 (4.5−13.5)
Median (interquartile range)	8 (7.2−8.5)
Platelet count (× 10,000)	
Mean ± SD (range)	14.3 ± 10.0 (2.8−34)
Median (interquartile range)	11.1 (6.9−17.4)
Prothrombin time (%)	
Mean ±SD (range)	63.1 ± 25.2 (15−103)
Median (interquartile range)	66 (43.1−82.6)
Activated partial thromboplastin time (s)	
Mean ±SD (range)	66.4 ± 41.8 (25.1−180)
Median (interquartile range)	54.4 (37.0−75)
International normalized ratio	
Mean ±SD (range)	1.56 ± 0.88 (1.02−4.94)
Median (interquartile range)	1.3 (1.08−1.67)

*Multiple clinical symptoms could be complained

**Anticoagulant therapy was applied in 18 patients

nine patients, and the ten remaining patients could not report any symptoms since they were under sedation (Fig. 2).

CE-CT was performed to confirm the presence of SRH using a 96- (SOMATOM Force; Siemens Healthcare, Forchheim, Germany [$n=2$]), 64- (Aquilion ONE or 64; Cannon Medical Systems, Otawara, Japan [$n=14$]), or 16-channel multidetector-row CT scanner (Brilliance-16; Philips Medical Systems, Best, Netherlands [$n=3$]). An unenhanced scan of whole body was obtained in transverse section. For the patients in whom SRH was detected on unenhanced images, dual-phasic CE-CT was fundamentally performed 30−45 and 100−120 s after intravenous administration of contrast material with 5 mm and 0.5−1.0 mm slice thickness. Iodinated non-ionic contrast material was injected at a dose of 510 mgI/kg of body weight with fixed injection duration of 30 s. Fifteen patients were obtained CE-CT examination less than 24 h before emergent angiography.

TAE procedure

Prior to the procedures, informed consent was obtained from all the patients or patients' families. After applying local anesthesia, 4- or 5-French (F) sheaths were introduced via common femoral artery. An aortogram of the abdomen and pelvis was obtained to find extravasation and involved arteries suspected on CE-CT, followed by a selective arteriogram of the first-order branches of the aorta, iliac artery, or femoral artery. Superselective catheterization of the branches was performed using a coaxial system using a 1.7−2.3-F microcatheter.

When the extravasation of contrast material was detected on the arteriogram, the microcatheter was advanced distally and the bleeding vessels were embolized. Gelatin sponge particles were the primary embolic agent of choice. Fibered

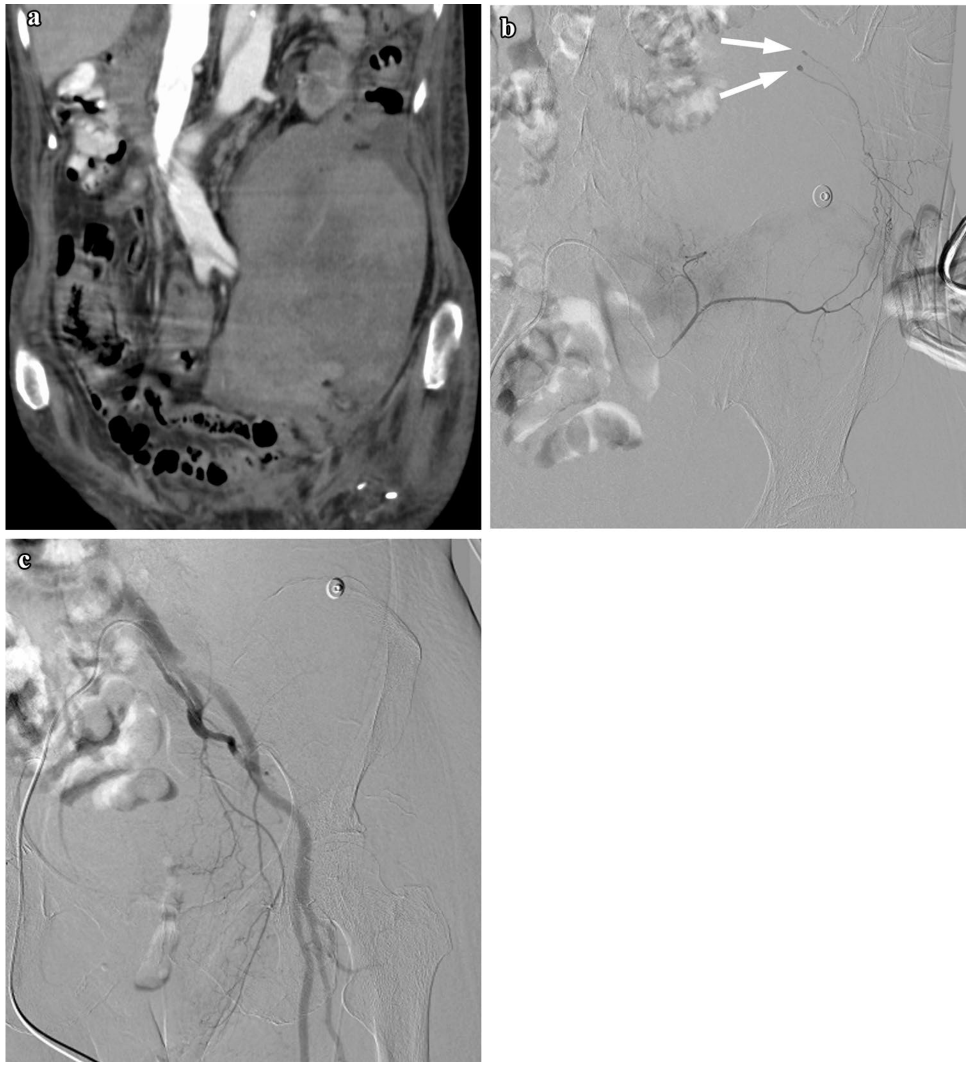

Fig. 2 A 76-year-old female who was anticoagulated for deep venous thrombosis developed spontaneous retroperitoneal hemorrhage. a Contrast-enhanced CT image shows retroperitoneal hemorrhage. However, no extravasation of contrast material is detected. b Selective left iliolumbar arteriogram demonstrates contrast extravasation (arrows). c Left internal iliac arteriogram after embolization of left iliolumbar artery and empiric embolization of left superior gluteal artery using gelatin particle show complete exclusion of embolized arteries

microcoils and *n*-butyl cyanoacrylate (NBCA) with iodized oil were used as embolic materials for the isolation of bleeding vessels according to the operators' discretion. In addition to the target arteries with active bleeding, other arteries that potentially distribute to the anatomic territory of the hematoma were catheterized and embolized to control active bleeding as much as possible via anastomoses. Even in the cases where extravasation of contrast material was not confirmed on angiography, the possibly involved arteries were empirically embolized using gelatin sponge particles, based on the location and territory of the hematoma observed on reference to the preoperative CT images.

Study analysis and definition

CE-CT imaging and angiographic findings, technical success and complication, and clinical success and outcome, were evaluated. The diagnostic performance of preoperative CE-CT for the detection of active bleeding was also assessed. Two readers (R.T. and M.H., with 12 and 8 years' experience) independently reviewed CE-CT images and recorded the location of the hematoma and signs of active bleeding. When active bleeding was identified, suspected bleeding sources were inspected and recorded on 0.5−1.0 mm reconstructed images. For the reading session, axial CT images were basically reviewed, and multiplanar reconstruction (MPR) images were supplementally constructed and referred using a dedicated picture archiving and communication (PACS) viewer (Yokogawa Solutions, Tokyo, Japan). The presence of extravasation from branches of the bleeding source at angiography was set as a reference standard.

Technical success was defined as successful embolization of the intended arteries with disappearance of extravasation and/or stagnation of the blood flow, and all the complications arising from the procedure were divided into major and minor categories according to the reporting standards of the Society of Interventional Radiology [17, 18]. Clinical success was defined as hemodynamic stabilization and sustained decrease or termination in transfusion compared with those before the procedure. Transfusion volumes of red blood cell (RBC) and frozen-fresh plasma (FFP) before and after the TAE were recorded. Follow-up, which consisted of clinical examination and laboratory testing, was performed as needed until the time of death or loss to follow-up.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD). To determine the diagnostic performance of CE-CT for the identification of active bleeding vessels, the following elements were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy with their 95% confidence intervals (CIs). The total units of RBC and FFP transfusion before and after the procedure were compared using the Wilcoxon signed-rank test. A p value of less than 0.05 was considered as statistically significant. Statistical analysis was performed using a statistical software (JMP version 11.0; SAS Institute Inc., Cary, NC, USA).

Results

CT and angiographic findings

Evidence of active bleeding both on CE-CT and angiography is summarized in Table 2. CT images could detect retroperitoneal hematoma formation in all the patients. Reader 1 observed active extravasation of contrast material in 15 patients (78.9%), while reader 2 observed it in 16 (84.2%). Furthermore, reader 1 detected indicated active bleeding in 31 arteries, while reader 2 detected it in 35. In 12 patients (63.2%), multiple active bleeding arteries were suspected by both readers.

Angiograms revealed active extravasation of contrast material in 37 arteries of 15 patients (78.9%). Multiple active bleeding arteries were identified in 10 patients (52.6%). On the other hand, no active bleeding was detected in four patients (21.1%).

For the detection of active bleeding, sensitivity and PPV were relatively high compared with specificity and NPV (Table 3). False-negative (failed to detect active bleeding) results were observed in two and one patient for reader 1 and 2, and false-positive (detected no extravasation on angiography) were observed in two patients each for both two readers. Accuracy for the detection of active bleeding was 78.9–84.2%, while that for the identification of the active bleeding arteries was 55.6–60.0%.

Table 2 Active bleeding findings both on contrast-enhanced CT and angiography, and embolized arteries

Bleeding sites	CE-CT		Angiography	
	Reader 1	Reader 2	Bleeding artery	Embolized artery
Lumber arteries	12	12	10	14
Iliolumbar arteries	9	11	10	11
Deep iliac circumflex arteries	7	7	6	9
Superior gluteal arteries	0	0	4	3
Intercoastal arteries	1	1	4	3
Inferior epigastric arteries	2	3	2	5
Superior vesical arteries	0	1	0	0
Lateral sacral arteries	0	0	1	1
Internal iliac arteries	0	0	0	1
Small anastomosis	0	0	0	1

Several arteries were prophylactically embolized despite the lack of active bleeding

Technical success and complication

Successful embolization of 48 intended arteries was achieved in all the patients including empiric embolization in four patients, yielding a technical success rate of 100%. Gelatin sponge particles were used in 18 patients, and the complementary use of 20–33% NBCA was carried out in three patients, and microcoils were used in four patients. In one patient, since the Adamkiewicz artery was visualized on a selective left third lumber arteriogram, microcoils were used to avoid spinal cord infarction. We did not encounter any major complications. Minor complications were observed in one patient (5.3%): transient neuropathy of right upper thigh in whom the right inferior epigastric artery, the right deep iliac circumflex artery, and the right iliolumbar artery were embolized.

Despite initial technical successful embolization, two patients required a second TAE 1 day after the first treatment. In a 64-year-old male who received TAE in the left lumber artery with gelatin sponge particles and 20% NBCA, his vital signs were unstable after receiving TAE and repeated angiograms demonstrated an additional extravasation from the left deep iliac circumflex artery. Hemostasis was achieved after the second TAE with 20% NBCA, but he developed intestinal bleeding 30 days after the first TAE and died of aspiration pneumonia 23 days later. There was also a 73-year-old man with multiple extravasations in the left lumber and intercostal arteries. These arteries were embolized with gelatin sponge particles, while the superior gluteal, deep iliac circumflex, and inferior epigastric arteries were empirically embolized with gelatin sponge particles. An additional embolization was requested because the patient

Table 3 Diagnostic performance for the contrast extravasation and identification of active bleeding arteries in contrast-enhanced CT

Variable	Reader 1	Reader 2
Identification of contrast extravasation		
Sensitivity	86.7% (13/15) (95% CI 77.8−94.5)	93.3% (14/15) (95% CI 84.6−98.6)
Specificity	50.0% (2/4) (95% CI 16.8−79.3)	50.0% (2/4) (95% CI 17.4−69.8)
Positive predictive value	86.7% (13/15) (95% CI 77.8−94.5)	87.5% (14/16) (95% CI 79.3−92.5)
Negative predictive value	50.0% (2/4) (95% CI 16.8−79.3)	66.7% (2/3) (95% CI 23.2−93.1)
Accuracy	78.9% (15/19) (95% CI 65.0−91.3)	84.2% (16/19) (95% CI 70.5−92.6)
Identification of active bleeding arteries		
Sensitivity	59.5% (22/37) (95% CI 49.5−68.3)	59.5% (22/37) (95% CI 49.4−69.2)
Specificity	60.9% (14/23) (95% CI 44.9−75.1)	50.0% (13/26) (95% CI 35.6−63.9)
Positive predictive value	71.0% (22/31) (95% CI 59.1−81.5)	62.9% (22/35) (95% CI 52.2−73.2)
Negative predictive value	48.3% (14/29) (95% CI 35.6−59.6)	46.4% (13/28) (95% CI 33.1−59.3)
Accuracy	60.0% (36/60) (95% CI 47.7−70.9)	55.6% (35/63) (95% CI 43.7−67.0)

Data are expressed as frequency (count). 95% CI 95% confident interval

required transfusion even after receiving TAE. Although the second TAE was performed from other left lumber arteries with 25% NBCA, he died of aspiration pneumonia 30 days after the procedure. Another patient developed abdominal compartment syndrome despite successful TAE with gelatin sponge particles, which was treated with surgical laparotomy 1 day after the TAE.

Clinical success and outcome

Hemodynamic stabilization and sustained decrease in transfusion were achieved in 17 patients (89.5%). The mean transfusion of RBC and FFP after the procedure significantly decreased from 10.1 (0−32) to 1.8 (0−10) and 7.8 (0−44) to 0.4 (0−4), respectively ($p < 0.001$) (Table 4). Clinical success could not be achieved despite the technical successes in the two aforementioned patients who developed clinical evidence of re-bleeding.

Complete follow-up was carried out in 15 patients and the remaining four patients were lost to follow-up; the mean follow-up duration was 624 ± 1118 days (range 8−3791 days). Six of 15 patients were discharged after the procedure and survived (range 58−3791 days). One patient (5.3%) died 30 days after the procedure due to aspiration pneumonia. Out of the remaining eight patients (42.1%), two died from pneumonia, while the other six each died from the following conditions: alveolar bleeding, sepsis, infectious endocarditis, liver failure, renal failure, and multiple organ failure.

Table 4 Blood transfusions before and after transarterial embolization

Variable	Before TAE	After TAE	*p* value
Red blood cell (units)			< 0.001
Mean ± SD (range)	10.1 ± 7.3 (0−32)	1.8 ± 2.9 (0−10)	
Median (interquartile range)	10 (6−12)	0 (0−2)	
Frozen-fresh plasma (units)			< 0.001
Mean ± SD (range)	7.8 ± 11.3 (0−44)	0.4 ± 1.1 (0−4)	
Median (interquartile range)	4 (0−11)	0 (0−0)	

Discussion

Spontaneous extraperitoneal hemorrhage frequently occurs in anticoagulated patients despite the absence of coagulopathy [15, 16]. The results of this study were in concordance with previous studies in which 94.7% of the patients underwent anticoagulation and only 27.8% developed coagulopathy. CT plays a pivotal role in the detection of SRH and its distribution, because clinical symptoms are frequently unclear due to the serious clinical status of patients under sedation [12–16]. In our study, CT revealed SRH in all the patients, although other clinical symptoms than hemodynamic instability and progression anemia could not be evaluated in 52.6% of the patients due to sedation. Contrast extravasation suggesting active bleeding was observed on CE-CT with desirable sensitivity (86.7−93.3%) and PPV (86.7−87.5%), which also concurs with previous papers [15, 16]. Our results also showed unsatisfactory specificity (50.0%) and NPV (50.0−66.7%). For this reason, CE-CT can be applied as the screening for the decision to perform angiography, while the absence of contrast extravasation does not mean we do not have to perform angiography. By contrast, the diagnostic performance of CE-CT for the accurate identification of active bleeding artery was not satisfactory. Dohan et al.[16] indicated that anticoagulation-related and intermittent bleeding is caused by spasm, hypotension, and soft tissue tamponade in elderly atherosclerotic patients. Moreover, SRH is associated with diffuse occult vasculopathy and arteriosclerosis of mircovessels in the retroperitoneal cavity that originally possess numerous collateral vessels in each territory [4–8]. Although these studies help to confirm our results that CE-CT can detect contrast extravasation, its ability to identify active bleeding vessels is insufficient.

The technical success rate of our study was 100% including multiple arterial embolization in 73.7% and empiric embolization in 21.1%, which concurs with previous studies [12–16]. Gelatin sponge particles alone were used to achieve complete hemostasis in 12 patients (70.6%). Gelatin sponge particles generally have risk for recanalization of the embolized arteries especially for patient with coagulopathy, and other embolic materials such as NBCA are recommended to achieve hemostasis [19, 20]. By contrast, SRH patients in the present study had transient coagulopathy that could be readily corrected by withdrawal of anticoagulant therapy or correction treatment for coagulopathy. This clinical situation in SRH patients enabled to use gelatin sponge as an embolic material, which is supported by previous papers that used gelatin sponge particles with complementary use of NBCA, PVA, and microcoil [12, 13, 15, 16]. Although the best embolic material for the treatment of SRH is a contentious issue, gelatin sponge particles are both effective and inexpensive [16]. In four patients, angiograms revealed no extravasation, which was empirically embolized. This situation occurred frequently in anticoagulation-related bleeding caused by unstable hemodynamic status [15, 16]. We believe that empiric embolization and embolization including possibly involved arteries surrounding the hematoma could control occult bleeding and minimize the risk of severe consequences, such as abdominal compartment syndrome, associated with large areas hematoma which occurred up to 50% in the previous studies [12, 15]. Urgent referral for endovascular therapy is also necessary when patients present hemodynamically unstable and/or progression of anemia despite receiving transfusion treatment.

Although the successful embolization of bleeding and possibly involved arteries was achieved, two patients failed to achieve clinical success, for reasons related to re-bleeding from other arteries. SRH is characterized by secondary ruptures of vessels caused by the enlargement of hematoma [4–6], and additional bleeding from other arteries develops despite complete embolization of affected arteries following the correction of coagulation status. Additionally, the hospital mortality rate (47.4%) and the 30-day post-treatment mortality rate (5.2%) are in line with previous publications [12–16]. This may be attributable to the poor clinical status of the elderly patients with multiple comorbidities. These findings highlight that complete embolization of affected arteries does not always lead to clinical success and preferable patient outcomes in the case of SRH.

Our study has some limitations. First, in addition to being a retrospective study, a control group is lacking. However, it is impossible to compare the present study to those regarding endovascular and conservative therapies, because of the rarity and emergent presentation of these patients. Second, the lack of long-term follow-up caused by the patients' short life expectancies prevented an exact evaluation of the efficacy and adverse effects of TAE. Lastly, findings of active bleeding through CE-CT and angiography may be influenced by several factors, including hypotension, soft-tissue tamponade effect, injection rate and duration of contrast material. Moreover, time intervals between CE-CT and angiography may have affected our results. However, these variabilities cannot be avoided due to the high emergency character of this condition.

In conclusion, transarterial embolization is technically safe and clinically effective treatment for patients with life-threatening spontaneous retroperitoneal hemorrhage. Although contrast-enhanced CT can confirm the presence of hematoma and contrast extravasation, accurate identification of affected vessels for active bleeding is insufficient. The inclusion of arteries that potentially distribute anatomic territory of the hematoma is an essential treatment strategy in the use of TAE.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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