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INTERVENTIONAL

Incidence and endovascular treatment of severe spontaneous non-cerebral bleeding: a single-institution experience

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Abstract

Objectives To investigate the incidence and endovascular treatment of severe spontaneous non-cerebral hemorrhage (SSNCH) in a high-volume, tertiary university hospital.

Methods All patients diagnosed with SSNCH between January 2016 and June 2017 were retrospectively analyzed. Endovascular treatment (group EVT) was offered only in patients demonstrating active bleeding at CT angiography (CTA). In cases without active bleeding at CTA, conservative management was decided (group CM). Outcome measures included the incidence of SSNCH, 6-month rebleeding, and survival rates in the two groups as well as EVT technical success and related complications.

Results Within the 18-month period, 44 SSNCH cases were identified, resulting in an annual incidence of 29.3 cases. In 37/44 cases (84.1%), bleeding was attributed to the antithrombotic therapy. In total, 19/44 patients underwent EVT (43.2%), and 25/44 patients (56.8%) were managed conservatively. Two patients who were initially treated conservatively finally underwent EVT due to rebleeding (7.4%). The technical success of EVT was 100%, while rebleeding occurred in 1 case (5.2%) following lumbar artery embolization and was successfully re-embolized. According to the Kaplan-Meier analysis, the 1-, 3-, and 6-month survival rates were 68.4%, 63.2%, and 42.1% for group EVT and 87.5%, 75.0%, and 58.3% for group CM, respectively. There were no EVT-related complications.

Conclusions The annual incidence of SSNCH in our institution is substantial. EVT resulted in uncomplicated, high bleeding control rates. The mortality rate was similarly high following either EVT or conservative treatment and was mainly attributed to severe comorbidities.

Key Points

- *This study demonstrates that the incidence of severe spontaneous non-cerebral hemorrhage (SSNCH) in our institution is substantial.*
- *Endovascular treatment was offered only in patients with clinical signs of ongoing hemorrhage and active bleeding at CT angiography and resulted in effective and uncomplicated, minimal invasive hemostasis, in a population with severe comorbidities.*
- *This is the first study to evaluate the outcomes of both endovascular hemostasis and conservative management. Rebleeding following either conservative or endovascular treatment was minimal.*

Keywords Hemorrhage · Therapeutic embolization · Anticoagulant drugs

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Abbreviations

CFA	Common femoral artery
CM	Conservative treatment
DSA	Digital subtraction angiography
EVT	Endovascular treatment
Hb	Hemoglobin
HU	Hounsfield units
LMWH	Low molecular weight heparin

MDCTA	Multi-detector computerized tomography angiography.
NOACs	New oral anticoagulants
NSAIDs	Non-steroid anti-inflammatory drugs
PFA	Profunda femoralis artery
SSNCH	Severe, spontaneous, non-cerebral hemorrhage
TAE	Trans-arterial embolization
vWF	von Willebrand factor

Introduction

Spontaneous bleeding is a life-threatening, clinical entity, strongly correlated with the administration of antithrombotic therapy [1, 2]. The term "spontaneous" refers to bleeding events unrelated with recognized trauma, recent surgery, or known underlying pathology [3, 4]. Antithrombotic therapy is one of the most common forms of medical intervention as it remains the mainstay of treatment and prevention of thrombosis in diverse clinical settings, including acute venous thromboembolism, atrial fibrillation, acute coronary syndromes, and invasive coronary or peripheral endovascular procedures [5, 6]. Notably, the omission of appropriate anticoagulant prophylaxis is a widely recognized medical error or malpractice [7]. Hemorrhage is the primary complication of anticoagulant therapy, even when maintained within recommended therapeutic ranges [8]. The reported annual incidence of major hemorrhagic complications due to oral anticoagulation intake ranges from 0.2–3% per patient per year [3]. The clinical indications for anticoagulation become more prevalent with older age; thus, this number is expected to rise due to the continuously increasing population age but also due to the widespread use of more potent antithrombotic therapy, including NOACs and antiplatelet agents such as ticagrelor and prasugrel [3–5, 9, 10]. Other risk factors for spontaneous bleeding include NSAIDs [11], hemodialysis (kidney failure stage 5 with GFR < 5 mL/h/1.73 m^2), and coagulation disorders (hemophilia B, anti vWF, thrombotic thrombocytopenic purpura, and autoimmune hemolytic anemia in conjunction with immune-mediated thrombocytopenia) [3]. Finally, diabetes mellitus [12] and acute lymphoblastic leukemia [3] have also been related to spontaneous bleeding events.

The clinical manifestation depends on the degree and rate of hemorrhage, while the diagnosis in the majority of the cases is confirmed by imaging using MDCTA, which is today considered the gold standard for the diagnosis of bleeding demonstrating excellent sensitivity and specificity of approximately 99%. The minimal bleeding detection rate of MDCTA is 0.3 mL/min [13, 14], which is lower than the 0.5 mL/min bleeding rate achieved by non-super-selective DSA [15].

Recently, an increase in the frequency of spontaneous bleeding has been reported and more aggressive management tactics have been described [4]. Nonetheless, the mainstream treatment currently relies on conservative measures such as rectification of coagulation parameters, fluid replacement, and blood transfusion [3, 4].

Endovascular treatment (EVT), mainly TAE and stent graft placement, is today considered a safe and effective treatment option for bleeding control, due to its minimally invasive nature and the high rates of rapid and durable hemostasis achieved even in high-surgical-risk patients [16, 17]. To date, the optimal treatment protocol for spontaneous bleeding remains controversial and concerns regarding overtreatment have been raised, while data demonstrating the mid-term efficacy of EVT remain scarce. Moreover, the incidence of severe, spontaneous, non-cerebral hemorrhage (SSNCH) is unknown. The purpose of this study was to assess the incidence of SSNCH and report the mid-term clinical outcomes following the conservative or endovascular treatment of SSNCH in a single institution.

Materials and methods

This study was approved by the Committee on Human Research of the institutional review board at our hospital and was compliant with the Health Insurance Portability and Accountability Act. Data from the hospital billing electronic database were retrospectively searched and collected. Search method was as follows: all CTA examinations (both images and radiological reports) performed between January 2016 and June 2017 were searched and those performed with the clinical finding of hematoma and/or bleeding were analyzed. Subsequently, all cases of spontaneous non-cerebral bleeding were recorded and further scrutinized, together with the patients' medical records, in order to confirm the diagnosis of SSNCH, by two individual radiologists with over 5 years of experience in MDCTA imaging (SS, AT). The investigators recorded the relative imaging details (presence and site of active bleeding, the presence and dimensions of hematoma, anatomical details, and final radiological diagnosis), demographical data, risk factors for bleeding, the treatment scheme (invasive or conservative), and patient follow-up during hospitalization and up to 6 months after the initial bleeding event. The electronic database of the interventional radiology unit was also searched for patients who underwent EVT and procedural details were recorded. In all patients, a CTA was performed using a 64-detector row CT (High Speed/Light speed General Electric). The hospital's CTA protocol includes non-enhanced CT, followed by an arterial and a portal-venous phase imaging, while a delayed 5-min phase was acquired only if deemed necessary. A hematoma was defined as an intermediate- to high-density inhomogeneous mass demonstrating an attenuation value of 60–80 HU, while active extravasation was defined as a focal high-density area within the hematoma with a CT attenuation value within 15 HU of the

aorta or major arterial branches during portal-venous-phase imaging as previously described [3]. Any disagreement was resolved by consensus. All patients or their relatives were personally contacted by phone by one of the investigators (AT), in order to confirm the follow-up data.

Patients with SSNCH were divided in two treatment groups. Group EVT included patients who underwent endovascular treatment (cessation of antithrombotic therapy and embolization or stent graft placement or both) and group CM included all patients who were managed conservatively (cessation of antithrombotic therapy, volume resuscitation, transfusion therapy, optimization of the coagulation profile, etc.). Direct treatment comparisons between EVT and conservative management in order to identify the superiority of one method over the other would not be meaningful, as the patients' clinical conditions were dissimilar, while the choice of treatment was case-sensitive and based on the fact that more severe SSNCH cases underwent EVT. The comparison of the overall survival rates are presented as an indicative measure of the prognosis expected following a SSNCH treated with either TAE or CM.

Definitions and outcome measures

Spontaneous bleeding was defined as a hemorrhagic event not related to trauma (iatrogenic included), surgery, or any underlying disease [3, 4]. The term "severe bleeding" was defined as a life-threatening bleeding characterized by one of the following criteria [17–19]: hemodynamic instability (systolic pressure < 90 mmHg or 40 mmHg lower than normal or signs of shock), need for transfusion with packed red blood cells due to Hb drop > 2 g/dL, Hb < 9 g/dL in patients with heart failure, acute coronary syndrome, or cardiovascular disease with evidence of tissue hypoxia, or Hb < 7 g/dL in all patients. The majority of the patients were hemodynamically stable (41/44; 93.2%) and 16/19 (84.2%) of the EVT cases were performed without general anesthesia.

The study's outcome measures were as follows: technical success defined as cessation of active extravasation on final selective DSA, according to international guidelines [20], the rebleeding and patients' survival rates in up to 6 months of follow-up, and the EVT-related complications. Survival was evaluated using the Kaplan-Meier analysis. Statistical analysis was performed with the GraphPad Prism software (GraphPad Prism, version 5.0).

Treatment protocol and trans-arterial embolization procedure

According to the hospital's protocol, the decision whether to treat the patient conservatively or to proceed with EVT was case-sensitive, based on various parameters such as the patient's age, medical history, comorbidities, clinical condition, laboratory tests, and CTA findings. CTA findings which were co-evaluated with the above factors included the detection of active contrast extravasation at the arterial, portal-venous, or delayed phase, the location of bleeding, size of hematoma, the presence of a growing hematoma in sequential imaging, and the diameter of the bleeding branch.

As all cases investigated in this study were judged as severe bleeding events, the main criterion as to proceed with EVT was the detection of active contrast extravasation at pre-procedural CTA and all cases that underwent EVT were positive for active bleeding at CTA. Patients with clinical signs of ongoing bleeding and negative CTA did not undergo DSA, but were investigated using further imaging which included sequential CTA imaging or endoscopic modalities as to exclude an ongoing bleeding missed by initial CTA. A hematoma presenting increased dimensions at sequential CT imaging was another criterion for embolization in patients with clinico-laboratory signs of ongoing bleeding.

The patients were transferred to the angiography suite under continuous monitoring and anesthesiology support. DSA was performed via a femoral or brachial artery access, according to the site of bleeding. All embolization procedures were performed in the angiography suite using a dedicated interventional angiography system (Infinix-i series, Toshiba Medical Systems).

The technique of embolization has been previously described elsewhere [3, 4]. In brief, an initial non-selective arteriogram was obtained with a 5-F pigtail catheter—or another appropriate diagnostic catheter—followed by selective arterial catheterization (usually of the lumbar, iliac, common femoral, deep femoral, or brachial arteries); in order to accurately detect the site of the bleeding, pre-procedural CTA imaging was used as guidance. Selective catheterization was performed with Simmons 1 or 2 catheter (Cordis), 5-F Cobra or Van Schie catheter or multipurpose catheter (Cook Inc). When necessary, microcatheters were used for super-selective catheterization (Progreat 2.7Fr; TERUMO) and the ASAHI Masters 2.6Fr (ASHAHI INTECC, CO). Embolization was performed using pushable coils or microcoils (Nestercoils, Cook) ranging from 2 to 8 mm, microspheres (Embozene microspheres; CELONOVA, PVA; Boston Scientific) ranging from 250 to 700 μm, *N*-butyl cyanoacrylate (Gluebran®, GEM SRL), in mixture proportions with lipiodol ranging from 1:2 to 1:4, gelfoam pledgets, or their combinations. The choice of the embolic agent was left at the discretion of the operator. Whenever required, the microcatheter was positioned distal to the bleeding site, and coil embolization was performed using the "back to front door" technique to avoid retrograde filling of the lesion. In cases in which super-selective catheterization of the bleeding vessel was not possible or the distal part of the lesion could not be negotiated, glue, gel foam, or microparticles were used to achieve distal penetration of the embolic agent and block retrograde filling.

Results

Within the 18-month study period, in total, 44 patients (female 23; 52.3%) with SSNCH were identified, resulting in an incidence of 29.3 cases per year. The mean patient age was 66 ± 16 years (range 25–92 years). The majority were rectus sheath ($n = 13$) and limb bleeding events ($n = 13$), followed by retroperitoneal ($n = 9$), intra-abdominal ($n = 5$), and thoracic/mediastinum ($n = 3$) bleeding events and one case of massive hemoptysis. In 84.1% of the cases (37/44 patients), the bleeding event was attributed to the antithrombotic therapy. In the remaining 7 events, risk factors such as hemodialysis ($n = 2$), liver disease ($n = 1$), lymphoma ($n = 1$), and diabetes with sepsis ($n = 1$) were present, while in one case, bleeding occurred in a female patient receiving hormonal replacement therapy, without any coexisting risk factors. In one case, bronchial artery bleeding occurred in a 39-year-old otherwise healthy female, without any medical history or risk factors for bleeding. As no underlying pathology was detected following extensive clinical and laboratory investigation, this bleeding event remained of unknown etiology. In total, 19/44 patients underwent EVT (group EVT; 43.2%), and 25/44 patients were managed conservatively (group CM 56.8%). The mean age in group EVT was 67.8 ± 16.0 years (range 32–88) and in group CM was 67.0 ± 16.9 (range 25–92). Two patients initially treated conservatively ($n = 2/27$; 7.4%), underwent embolization due to rebleeding at the rectus sheath demonstrated with sequential CTA, while one patient with thigh hematoma and active bleeding from a PFA branch at initial CTA was not embolized as the intra-procedural DSA was negative for bleeding and was treated conservatively. Most of the patients in group EVT (11/19; 57.9%) were under antithrombotic therapy with LMWH, as monotherapy (7/19; 36.8%), or in combination with antiplatelet therapy (3/19; 15.7%), while only three patients were receiving LMWH at therapeutic doses (Table 1). In 5/19 cases (26.3%), patients were receiving vitamin K antagonists (warfarin or acenocoumarol), and in two cases (10.5%), no antithrombotic therapy was administrated. The majority of the patients included in group CM (9/25; 36.0%) were under antiplatelet therapy (single 6/25; 24% and dual 3/25; 12.0%). Vitamin K antagonists were used in 7/25 patients (28.0%) and heparin in 5/25 patients (20.0%) LMWH was administrated (two in therapeutic dose). One patient (4%) was receiving rivaroxaban 2.5 mg twice daily. Three patients (12.0%) were not receiving any antithrombotic therapy. The mean body mass index (BMI) was 29.4 in group EVT and 30.8 in group CM. The patients' demographical data, antithrombotic therapy, a short description of the bleeding event, and the final outcome are analytically reported in Tables 1 and 2.

EVT technical success was 100%. Rebleeding occurred in 1/19 case (5.2%) 1 day following lumbar artery embolization (4th and the 5th lumbar arteries). Rebleeding was due to spontaneous hemorrhage of the 3rd lumbar artery which was successfully embolized. TAE was performed in all EVT cases while in two cases (2/19; 10.5%) additional stent graft deployment was performed. The rebleeding rates between the two groups were similar (group EVT 5.2% vs. group CM 7.4%; $p = 0.38$). The mean hematocrit value before EVT was 27.85 ± 6.2 and increased to 28.04 ± 6.2 1 day after the procedure. According to the Kaplan-Meier analysis, the estimated 1, 3, and 6-month survival rates were 68.4%, 63.2%, and 42.1% in group EVT and 87.5%, 75.0%, and 58.3% in group CM, at 1, 3, and 6 months; respectively ($p = 0.23$; Fig. 1). No EVT-related complication was noted.

Rectus sheath hematomas

Among 13 patients with rectus sheath hematomas, nine underwent EVT (69.2%) and five were managed conservatively (38.5%). All patients who underwent embolization demonstrated active contrast extravasation at CTA and all patients in group CM did not demonstrate active contrast extravasation at CTA. All but two patients were hemodynamically stable (12/13; 92.3%). All unstable patients were stabilized by the anesthesiology team with the use of inotropic drugs and fluid support and transfusions and underwent embolization under general anesthesia. The remaining cases underwent embolization using sedation and local anesthesia.

Embolization of the inferior epigastric artery (IEA) was performed via retrograde contralateral ($n = 5$) or homolateral ($n = 4$) common femoral artery approach. An initial DSA was performed with a pig tail catheter at the level of the common Iliac artery to detect the bleeding and grossly exclude any involvement of branches of the common femoral, internal, or external iliac arteries. Subsequently, a *Van Schie* or Cobra catheter was placed at the origin of the IEA and selective catheterization of the vessel was performed with the use of a microcatheter. Embolization agents used were microcoils ($n = 5$), glue ($n = 2$), microcoils and glue ($n = 1$, Fig. 2), and microcoils with gelfoam ($n = 1$). The 30-day mortality rate was 11.1% (1/9 patients) in group EVT and 0% in group CM. Rebleeding rate was 0% for group EVT and 7.4% for group CM ($p = 0.11$).

Retroperitoneal bleeding

A retroperitoneal SSNCH was detected in eight cases, six due to lumbar artery bleeding (66.6%) and three from other vessels (external iliac artery branches; $n = 1$, internal iliac artery branches; $n = 2$, renal artery branches; $n = 1$). In total, 4/8 patients (50%) underwent embolization (3 cases of lumbar arteries bleeding and 1 renal artery branches bleeding). The arterial access for embolization was obtained by the right CFA in all cases. The 30-day mortality rate was 25% for the EVT group (1/4 cases) and 0% for patients in group CM. The material

Table 1 Demographical data, antithrombotic therapy, bleeding event description, and final outcome measure of patients in the endovascular treatment group

No.	Age (year)	Gender	Comorbidities	Antithrombotic therapy	CT description	Cause of death
1	80	F	Congestive heart disease, DM	LMWH	Left rectus sheath hematoma with intra-pelvic extension; active bleeding; MD 8.9 cm	Septic shock
2	76	F	HF, hypertension, DM, sepsis	None	Left psoitis muscle hematoma and active bleeding; MD 20 cm	Septic shock
3	86	F	HF	LMWH	Retroperitoneal multiple small active bleeding foci; MD 19.4 cm	Cardiac arrest
4	88	F	Major stroke, HF, dementia	Therapeutic LMWH	Massive intramuscular left axillary region/lateral thoracic wall hematoma with active bleeding foci; MD 14.2 cm	Endocarditis
5	59	F	Lupus, dialysis, sepsis, pulmonary hypertension	LMWH	Active bleeding and hematoma in left axillary region; MD 17.3 cm	Septic shock
6	60	F	Dialysis, hepatorenal syndrome	LMWH	Soft tissue hematomas in medial surfaces of the thighs bilaterally. Active bleeding foci at the left thigh; MD 19.8 cm	Cardiac arrest
7	68	F	Major ischemic stroke, AF	LMWH/clopidogrel 75 mg	Left rectus sheath hematoma with two active bleeding foci; MD 7.3 cm	Alive
8	33	M	Lupus, cecal bleeding surgically treated 1 year ago	LMWH	Lt peri-renal hematoma with active bleeding; MD 11.1 cm	Alive
9	64	M	CAD, hypertension	Acenocoumarol 4 mg	Lt PFA branches; MD 9.4 cm	Alive
10	53	M	Cardiac arrest	Therapeutic LMWH	Retroperitoneal hematoma and active bleeding; MD 6.1 cm	Cardiac arrest
11	85	F	ICU for MI	ASA 100 mg/ticagrelor 60 mg/LMWH	CTA active bleeding from Lt PFA branches; MD 10.3 cm	Septic shock
12	74	F	HF (cardiac output 15%), metallic valve	ASA 100 mg/acenocoumarol 4 mg	Lt Rectus sheath hematoma not penetrating the muscle fascia. Active bleeding; MD 15.2 cm	Cardiac arrest
13	39	F	No medical history. Massive hemoptysis > 500 mL	None	Alveolar bleeding within the middle and right lower lobe, bronchial arteries < 2 mm	Alive
14	53	F	AF	Warfarin	Rectus sheath hematoma. Multiple active bleeding foci; MD 19.6 cm	Alive
15	65	F	Valvular heart disease	Warfarin	Right rectus sheath hematoma; active bleeding; MD 17 cm	Alive
16	81	F	Dialysis	LMWH	Right rectus sheath hematoma with active bleeding foci; MD 14 cm	Alive
17	82	F	Dialysis	None	Lt rectus sheath hematoma and active bleeding; MD 16 cm	Alive
18	76	F	Acute renal failure, urinary tract infection, MI, urinary bladder rupture, intestinal perforation, metabolic acidosis	Warfarin	Lt rectus sheath hematoma with intra-pelvic extension and active bleeding; MD 18.1 cm	Metabolic acidosis
19	32	M	DVT, elevated transaminase levels, hepatitis C	Therapeutic LMWH	Right rectus sheath hematoma with intra-pelvic extension; MD 12 cm	Alive

HF heart failure, *DM* diabetes mellitus, *LMWH* low molecular weight heparin, *CAD* coronary artery disease, *AF* atrial fibrillation, *ASA* acetylsalicylic acid, *ICU* intensive care unit, *MD* maximum diameter

Table 2 Demographical data, antithrombotic therapy, CT description, and final outcome measure of patients in the conservative treatment group

No.	Age (years)	Gender	Comorbidities	Antithrombotic therapy	CT description	Cause of death
1	58	M	Stroke	LMWH/clopidogrel 75 mg	Right axillary region/anterior thoracic wall hematoma; MD 11.9 cm	Alive
2	75	M	Non-Hodkin lymphoma	None	Peri-splenic hematoma; MD 13.5 cm	Alive
3	84	M	AF, COPD	Acenocoumarol 4 mg	Retroperitoneal hematoma; MD 11 cm	Septic shock
4	69	F	Colorectal liver metastasis under chemotherapy. Cardiac insufficiency, CAD	Clopidogrel 75 mg ASA 100 mg	Soft tissue hematoma of the right thigh; MD 13.5 cm	Septic shock, cardiac arrest
5	84	M	AF	Rivaroxaban	Retroperitoneal hematoma; MD 22 cm	Cardiac arrest
6	56	F	Sepsis, melenas	Acenocoumarol 4 mg	Left femoro-inguinal hematoma; MD 9.5 cm	Hemorrhagic shock after gastroscopy
7	77	M	AF, COPD	Acenocoumarol 4 mg	Right rectus sheath hematoma; MD 8 cm	Alive
8	50	M	Elevated transaminase levels/hepatosplenomegaly	ASA 100 mg	Morison's pouch hematoma; MD 7.5 cm	Alive
9	49	F	Hormonal replacement therapy	None	Right iliac fossa hematoma; MD 7.2 cm	Alive
10	92	F	Cardiac failure, hypertension, dementia	ASA 100 mg	Right pectoralis (major and minor) hematoma; MD 6.3 cm	Cardiac arrest
11	60	M	Cirrhosis, anemia	None	Perihepatic hematoma; MD 10 cm	
12	68	M	CAD	ASA 100 mg	Right thigh/inguinal hematoma; MD 5.4 cm	Septic shock
13	69	F	CAD, diabetes, hypertension	Therapeutic LMWH	Crural soft tissue hematoma: MD 4.2 cm	Alive
14	62	M	Lung Ca, AF, thrombocytopenia	LMWH	Latissimus dorsi and anterior serratus muscle hematoma; MD 5 cm	Alive
15	70	F	Hypertension, coronary bypass	Clopidogrel 75 mg	Intrahepatic hematoma; MD 4 cm	Cardiac arrest
16	56	F	Hypertension, AF	Acenocoumarol 4 mg	Anterior mediastinum hematoma; MD 4.5 cm	Alive
17	25	F	Metallic aortic valve, dialysis	LMWH	Anterior mediastinum hematoma; MD 9.5 cm	Alive
18	64	M	DM, CAD	Prasugrel 5 mg	Anterior mediastinum peri-aortic hematoma; MD 7.5 cm	Alive
19	90	F	Dementia, depression, CAD, HF	Salospir 100 mg	Right retroperitoneal/ peri-renal hematoma; MD 15 cm	Septic shock
20	79	F	CAD, hypertension	Acenocoumarol 4 mg	Quadriceps femoris hematoma; MD 7.3 cm	Alive
21	77	M	CAD, hypertension	ASA 100 mg/clopidogrel 75 mg	Right rectus sheath hematoma; MD 8 cm	Alive
22	82	M	CAD	ASA 100 mg	Retroperitoneal hematoma; MD 12 cm	Alive
23	64	F	Valvular heart disease	Acenocoumarol 4 mg	Intrahepatic and right internal oblique muscle hematoma; MD 12 cm	Alive
24	82	M	Urinary bladder cancer	Acenocoumarol 4 mg	Right major teres muscle hematoma, MD 18 cm	Alive
25	75	M	Dialysis, hypertension	None	Right rectus sheath hematoma; MD 8.3 cm	Cardiac arrest

LMWH low molecular weight heparin, *CAD* coronary artery disease, *AF* atrial fibrillation, *COPD* chronic obstructive pulmonary disease, *HF* heart failure, *DM* diabetes mellitus, *ASA* acetylsalicylic acid, *MD* maximum diameter

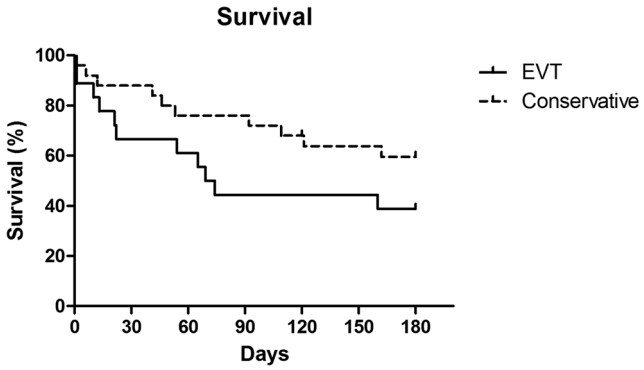

Fig. 1 Kaplan-Meir plots of patient survival in groups EVT and CM

used for embolization was solely glued in the lumbar artery embolization cases. Glue and microcoils were used for hemostasis in the renal artery branches bleeding case.

Limb hematomas

In total, ten patients presented with severe upper ($n = 2$) and lower ($n = 8$) limb hematomas and 5/11 patients (50%) underwent EVT. Specifically, in the three bleeding cases involving branches of the PFA, one was embolized using microcoils and glue (Fig. 3), one using microcoils only, and one using gelfoam for the embolization of bilateral PFA branches in a single session. Embolization using microcoils ($n = 1$) and 500 μm microparticles ($n = 1$) with additional stent graft placement was performed in two SSNH cases from axillary (Fig. 4) and brachial artery branches respectively. The technical success rate was 100%, without complications, while no patient underwent surgery for compartment syndrome. The 30-day mortality rate was 2/5 in the EVT group (40%) and 1/8 (12.5%) in the CM group. No rebleeding occurred in both groups.

Spontaneous hemoptysis

One case of spontaneous, massive, life-threatening hemoptysis (over 500 mL) occurred in a 39-year-old female, without any medical history and no risk factors for bleeding. Furthermore, the CT examination failed to identify any cause related to the event. The patient was intubated and initially managed with bronchoscopy which failed to achieve hemostasis. Subsequently, a Fogarty balloon was inflated as the patient became hemodynamically unstable during the bronchoscopy. The patient was immediately transferred to the angiography suite. Following right CFA access and superselective catheterization of the right bronchial artery, using a microcatheter, DSA identified the "cut-off" sign involving a small bronchial branch at the area of interest, just adjacent to the Fogarty catheter. Embolization using a 2 × 50 mm microcoil was successfully performed (Fig. 5). Bronchoscopy and biopsy 3 weeks after embolization did not reveal any underlying disease and the patient is hemoptysis-free at 16 months of follow-up.

Inta-abdominal bleeding

We recorded five intra-abdominal SSNCH cases. To be more specific, one perihepatic, one intrahepatic and one posterior right subhepatic space (Morison's pouch) hematoma, one right iliac fossa hematoma in a female patient under hormonal replacement therapy and no other comorbidities, and one perisplenic hematoma in a patient with lymphoma. All cases were treated conservatively, as no active bleeding was noted at CTA. The 30-day mortality was 20% (1/5 cases) as one patient died (Morison's pouch hematoma). No further bleeding was noted in the remaining cases.

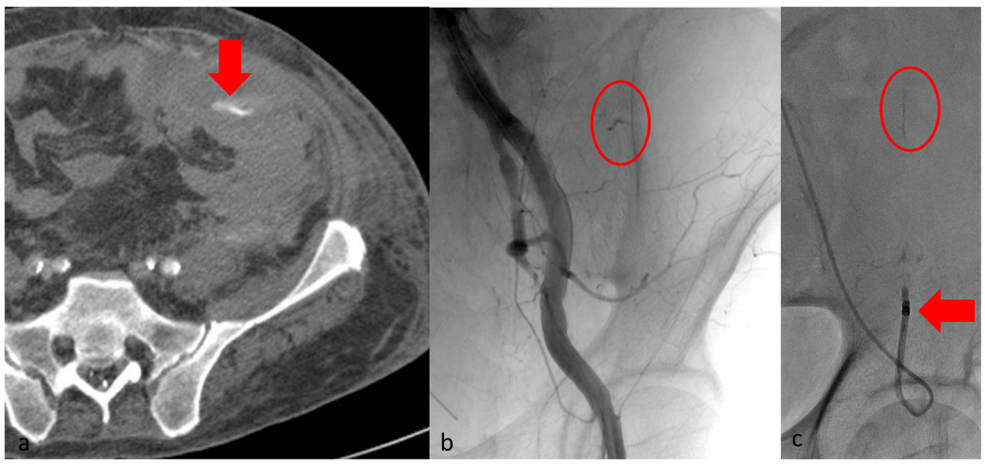

Fig. 2 Patient hemodynamically unstable (stabilized by the anesthesiology team) and significant 10 units Ht drop. **a** CTA demonstrating large rectus sheath hematoma and active bleeding from the left inferior epigastric artery (arrow). **b** DSA from the left external iliac artery demonstrating the bleeding site from the left inferior epigastric artery. **c** Catheterization of the left inferior epigastric artery using a Van Schie 5Fr catheter and a microcatheter and subsequent embolization of the bleeding using glue (circle) and a single 3 × 70 mm microcoil (arrow)

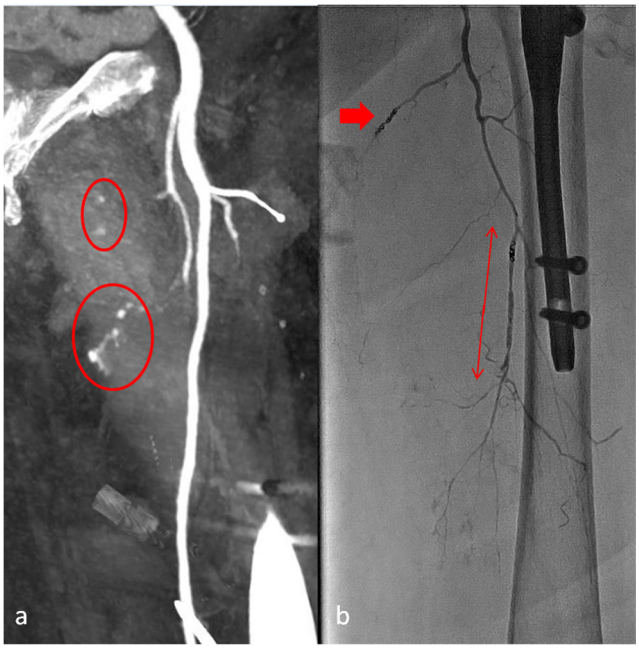

Fig. 3 Hemodynamically stable patient with a large nearly 10 cm left thigh hematoma and 8 units Ht drop. **a** Coronal, maximum-intensity projection (MIP) CTA image demonstrating a thigh hematoma with multiple foci (circles) of active bleeding from two profunda femoralis artery (PFA) branches. **b** Selective microcatheter catheterization and embolization using glue (arrowhead) and microcoils (arrows) of both PFA branches

Truncal hematomas

We noticed six cases of spontaneous thoracic, mediastinum, or dorsum hematomas. Specifically, one anterior mediastinum/peri-aortic hematoma, two in anterior mediastinum hematomas, one latissimus dorsi and anterior serratus muscle hematoma, one right pectoralis (major and minor) hematoma, one right major teres muscle hematoma, and one right axillary region/anterior thoracic wall hematoma. No active bleeding was present at CTA and all cases were managed conservatively. All patients were alive at 6 months of follow-up, while no rebleeding episodes were noted.

Discussion

The results of this study demonstrate that in our hospital, severe, spontaneous, non-cerebral hemorrhage is a common, life-threatening pathology. Moreover, the annual incidence of nearly 30 cases noted in our institution (over two cases per month) is expected to increase in the upcoming years due to continuously growing use of novel, more potent, antithrombotic drugs. As herein presented, nearly 50% of the patients suffering from SSNCH were not treated conservatively and were offered a more aggressive, but still minimal invasive, endovascular treatment option. Notably, the technical success of EVT was 100%. Due to the complexity of these cases, often presenting severe and numerous comorbidities such as atrial fibrillation, metallic heart valves, coronary stents, and diabetes mellitus, the choice of treatment must be personalized and should be decided by a multidisciplinary team consensus.

In this study, only one case of rebleeding was noted and was successfully treated with further coil embolization. However, rebleeding occurred at the 3rd lumbar artery, while

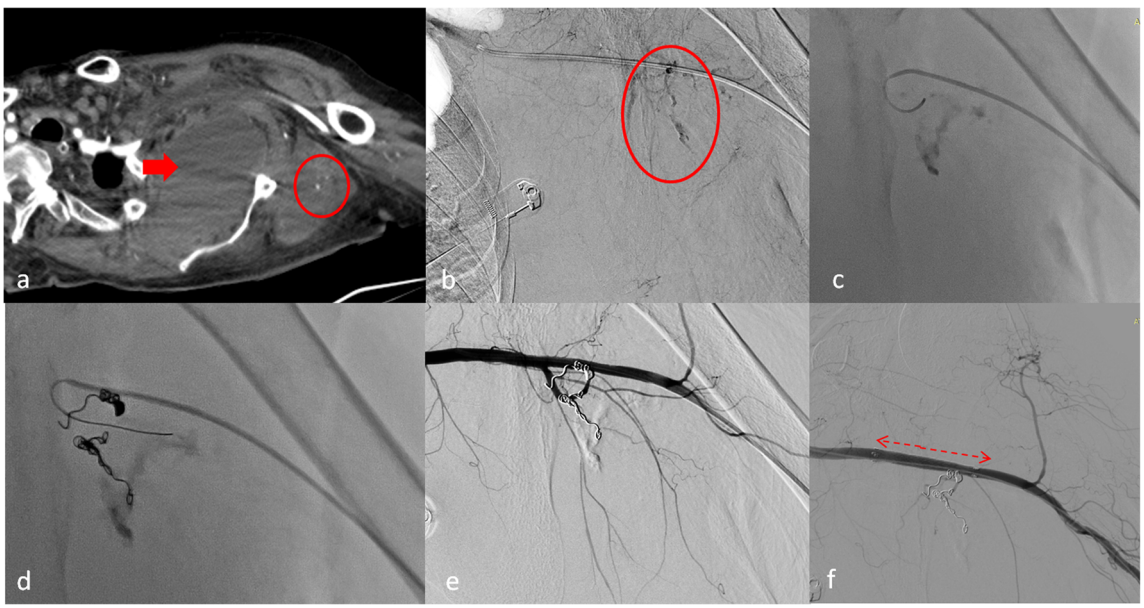

Fig. 4 Hemodynamically stable patient with a 14.2-cm intramuscular left axillary/lateral thoracic wall hematoma and 9 units Ht drop. **a** Axial MIP image demonstrating the hematoma (arrow) and active bleeding foci (circle). **b** Arterial access and DSA from the left brachial artery demonstrating the bleeding site (circle). **c** Selective catheterization of the left lateral thoracic artery branches (**d**) and microcoil embolization (**e**). DSA demonstrating remaining patency of the embolized branches (**f**) further treated with a 8 × 60 cm stent graft (arrow)

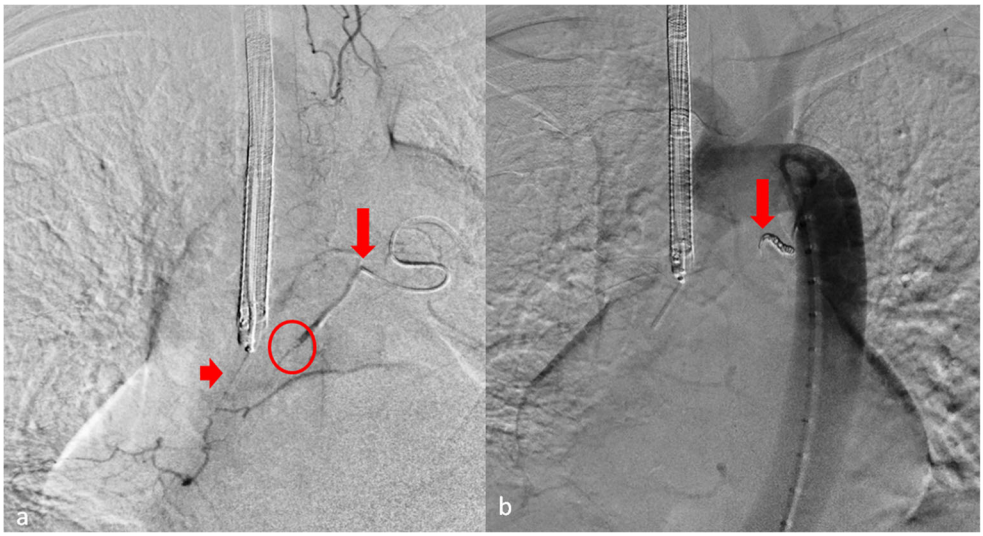

Fig. 5 A 38-year-old female patient presenting with spontaneous massive hemoptysis causing an Ht drop of 9 Units. The patient was intubated and a Fogarty catheter was inflated during bronchoscopy as massive bleeding continued causing hemodynamic instability. **a** Selective catheterization of the right bronchial artery with a microcatheter (arrow) and DSA depicting the "cut-off" sign (circle) at the region of the Fogarty catheter (short arrow) indicating the abrupt discontinuation of a small bronchial artery branch due to spasm (also known as the "cut-off sign"). **b** Microcoil embolization of the bronchial artery branch (arrow) achieving hemostasis at final DSA

the 4th and the 5th were previously embolized. It is not perfectly clear whether this was missed at initial embolization or another bleeding occurred at a different level. The authors decided to consider this as a rebleeding event. The technical success, rebleeding, and 1-month mortality rates are similar to previous reports of EVT for spontaneous bleeding [3, 4, 21]. In two cases, bleeding relapse occurred during CM. Those patients underwent successful embolization. On the other hand, one case of active bleeding from branches of the PFA demonstrated with CTA was finally not embolized as no arterial bleeding was detected following selective DSA. This could be attributed to the immediate discontinuation of antithrombotic therapy and the correction of the coagulation profile. It is imperative that referring physicians immediately withdraw antithrombotic therapy upon the suspicion of bleeding and CTA should be performed after the appropriate actions to correct the patient's coagulation and hemodynamic status (plasma, vitamin K, etc.) have been taken, in order to support the cascade of natural hemostasis and avoid unnecessary invasive procedures.

EVT was offered in almost all cases of SSNCH demonstrating active arterial bleeding at CTA. Specifically, in this study in which bleeding was considered severe, all patients with arterial bleeding, identified at CTA, underwent embolization. To our experience, non-severe, CTA-proven, ongoing arterial bleeding can be managed conservatively only in specific anatomical locations which can contain the volume of blood loss, such as the rectus sheath or gluteal region. According to the authors' opinion, a personalized treatment algorithm offering CM or EVT according to the severity of clinical presentation, the anatomical location of the bleeding and the patient's single characteristics, is required to optimize treatment outcomes and reduce overtreatment. Given the fact that only severe, life-threatening, spontaneous bleeding was investigated in the present study, the main criterion in order to proceed to EVT was an active contrast extravasation detected with CTA. One could argue that some of these cases, especially rectus sheath hematomas, could have been managed conservatively, and that hemostasis could have been achieved following discontinuation of antithrombotic therapy and hemodynamic support. Popov et al, in order to address the issue of overtreatment, has proposed a treatment algorithm for rectus sheath bleeding. Specifically, the authors performed embolization in patients demonstrating active bleeding and muscular fascia rupture (type III), or active bleeding without muscular fascia rupture but with a contraindication to discontinue the anticoagulation therapy (type IIb) or those not receiving anticoagulation at all (type IIc), while conservative treatment was suggested in cases without active bleeding at CTA or those with active bleeding in which the anticoagulation therapy could be discontinued (type IIa) [4]. The only difference between the protocol followed in the present study and the Popov algorithm is that embolization was performed even in type IIa rectus sheath bleedings. The authors consider inferior epigastric artery embolization as a minor, not technically demanding, endovascular procedure, which can be performed rapidly and rarely resulting in ischemic complications. Therefore, the implementation of a conservative approach which entails the risk of further hemodynamic compromise, especially in the elderly with severe comorbidities, requires significant amounts of precious blood products and probably increases ICU hospitalization time and should be balanced

against the strategy of prompt IEA embolization. Notably, these patients will eventually restart antithrombotic therapy and there is great uncertainty regarding the possibility of bleeding relapse. Comparative studies to address these issues are not currently available in the literature.

Limbs are also anatomical locations in which the volume of blood loss can be confined by the robust muscular structures within a small area and therefore CM would be an option, even in cases of active bleeding. However, expanding limb hematomas can lead to compartment syndrome and decompression surgery, which would be further complicated by the presence of active extravasation. In cases of retroperitoneal, intra-abdominal and pulmonary SSNCH, the decision not to proceed with EVT in the existence of active bleeding has never been described and CM is generally not recommended.

Another treatment option would be open surgical hemostasis. In this study, no patient underwent surgery for SSNCH and this was a multidisciplinary team decision. Despite the fact that studies comparing open surgical with endovascular hemostasis for SSNCH are missing, the high technical success and minimal invasive nature of EVT, renders the randomized comparison of the two methods very difficult. The authors believe that more aggressive treatment algorithms should be considered for SSNCH, and prompt EVT should be offered in cases of ongoing arterial bleeding detected by CTA, as to avoid further hemodynamic compromise especially in patients with significant comorbidities, but also in cases in which quick anticoagulation therapy resume is vital in order to decrease the risk of fatal thromboembolic complications.

SSNCH events from renal artery and bronchial artery branches were also noted in this study. Such cases remain sporadic in the literature [22, 23]. Both cases were promptly diagnosed and treated with trans-arterial embolization. Another particularity of this study is the fact that many different endovascular devices and embolic materials have been used, in a large variety of anatomical locations, while similar technical success rate was noted between various embolic materials used (Table 3). This further supports the notion that in experienced hands, the correct choice of embolic material results in high, uncomplicated, hemostasis rates [3]. Nonetheless, in the vast majority of the cases, the authors have used permanent embolic materials, while gel foam, a temporary embolic material, was used as a sole embolic agent only in one case of diffuse bilateral PFA embolization, mainly due to concerns about rebleeding following absorption of the material.

It should also be highlighted that SSNCH occurred in 7 patients who were not receiving any anticoagulation therapy, as well as in one patient without any medical history or known risk factor. SSNCH not correlated with antithrombotic therapy or risk factors such as diabetes, dialysis, hypertension, or sepsis is a very rare event and its mechanism, which probably entails some degree of vascular-microvascular abnormality, remains to be determined [24].

The main limitation of this study is the retrospective, single-center design. Due to the retrospective data analysis, some SSNCH cases might have been missed, while the reliability of the follow-up is not optimal. Moreover, the search method allowed the identification of SSNCH cases that were

Table 3 Vessels embolized and embolic material used in patients of group EVT

No.	Vessel embolized	Embolic agent
1	Left IEA and IIA branches	Gel foam and microcoils
2	Left 1st/2nd lumbar arteries	Glue (mixture 1:4)
3	Left 4th/5th lumbar arteries	Glue (mixture 1:3)
4	Left axillary artery branches	Microcoils/8 × 40 stent graft
5	Left brachial artery branches	500-μm microspheres/8 × 40 stent graft
6	Bilateral PFA branches	Gel foam
7	Left IEA	Microcoils
8	Left renal artery branches	Glue (mixture 1:3) and microcoils
9	Left PFA branches	Glue (mixture 1:3) and microcoils
10	Right lumbar artery	Glue (mixture 1:3)
11	Left PFA branches	Microcoils
12	Left IEA	Microcoils
13	Right bronchial artery branch	Microcoil
14	Right IEA	Microcoils
15	Right IEA	Microcoils
16	Right IEA	Glue (mixture1:3)
17	Left IEA	Microcoils
18	Left IEA	Glue (mixture 1:3) and microcoil
19	Right EIA	Glue (mixture 1:2)

IEA inferior epigastric artery, *PFA* profunda femoralis artery, *IIA* internal iliac artery, *EIA* external iliac artery

referred for CT imaging. However, in our hospital, severe bleeding cases not referred for CT imaging are extremely uncommon, and therefore, very few cases would have been omitted from the analysis. Furthermore, as this was a single-institution study, the reproducibility of the results remains uncertain. Other significant limitations influencing the statistical validity of this study are the relatively small number of patients included in the embolization group and the heterogeneity of the procedures which were performed in several different anatomical locations using different technical approaches (embolic agents, stent grafts, catheters, etc.). Finally, the study was not designed to allow a direct comparison between conservative management and EVT comparison, which nevertheless was beyond the scope of this study.

In conclusion, the incidence of SSNCH in our institution is substantial. EVT resulted in uncomplicated, high bleeding control rates. Mortality rates were similarly high following either EVT or conservative treatment and were mainly attributed to severe comorbidities. The low rate of EVT-related complications and the need to rapidly restart anticoagulation should encourage a lower threshold for EVT.

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Compliance with ethical standards

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

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all patients in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Case-control study
- Performed at one institution

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