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Endovascular Treatment of Renal Bleeding: Technical Success, Clinical Tolerability and Overall Success

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Osman Öcal

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Erster Gutachter:	Prof. Dr. med. Max Seidensticker
Zweiter Gutachter:	Priv. Doz. Dr. Harun Ilhan
Dritter Gutachter:	apl. Prof. Dr. Ricarda Bauer
ggf. weitere Gutachter:	____________________________________

Mitbetreuung durch den promovierten Mitarbeiter:	Prof. Dr. med. Max Seidensticker
Dekan:	Prof. Dr. med. Thomas Gudermann

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Zusammenfassung:

Nierenblutungen sind relativ selten, können jedoch lebensbedrohliche Auswirkungen haben und erfordern daher eine schnelle Diagnose und Behandlung. Die Hauptursachen für Nierenblutungen sind Traumata, Biopsien, partielle Nephrektomien und spontane Rupturen von Nierentumoren. Bei Vorliegen eines Hämatoms der Niere und fehlendem Nachweis einer aktiven Blutung (i.d.R. verifiziert durch eine Computertomographie), ist häufig eine konservative Behandlung ausreichend; sollte jedoch eine aktive Blutung nachgewiesen werden, ist i.d.R. eine Intervention (Operation/Embolisation) erforderlich, insbesondere vor dem Hintergrund, dass z.B. postoperativ keine suffiziente Tamponade mehr durch den Fasziengürtel zu erwarten ist. Obwohl die minimal invasive Therapie von Blutungen mittels interventoniell radiologischer, selektiver Embolisation sich als wirksame und schonende Therapie im Allgemeinen etabliert hat, fehlt es an detaillierten Studien zur Untersuchung ihrer Wirksamkeit und Sicherheit in der Therapie von Nierenblutungen. Das Ziel der vorliegenden Arbeit ist es, die technische und klinische Effektivität der interventionell radiologischen Embolisation von Nierenblutungen und deren Sicherheit im Rahmen einer retrospektiven Datenanalyse zu evaluieren.

Die elektronische Datenbank des Krankenhauses wurde nach allen Patienten durchsucht, die zwischen Januar 2010 und Juni 2020 eine Nierenarterienembolisation erhalten haben. Alter, Geschlecht, Symptome, Nierenfunktionstestergebnisse, Befunde vor dem Eingriff, Verfahrensmerkmale, Kontrastmitteldosis, Follow-up-Befunde inkl. Nierenfunktionstests wurden retrospektiver dokumentiert.

Bei 76 Patienten (mittleres Alter 67.3 Jahre) wurden 86 Nierenembolisationsprozeduren durchgeführt. 80/86 (92.8%) Interventionen waren primär technisch erfolgreich. Die Nierenarterienembolisation war bei 72 von 76 Patienten (94.7%) klinisch erfolgreich.

Risikofaktoren für ein klinisches Versagen waren die Einnahmen von Thrombozytenaggregationshemmern ($p = 0,033$) und technisches Versagen ($p <0,001$). Eine multivariable Analyse identifizierte das technische Versagen als den einzigen signifikanten Risikofaktor, während die Einnahme von Thrombozytenaggregationshemmern geringfügig nicht signifikant war ($p = 0,051$). Nur ein Patient (1,3%) musste aufgrund von refraktären Blutungen einer Nephrektomie unterzogen. Nach 16 (21%) Eingriffen wurde eine akute Nierenfunktionsstörung (definiert als Anstieg des Serumkreatininwerts von ≥ 0,3 mg/dl innerhalb von 2 Tagen) beobachtet. Risikofaktoren für eine akute Nierenfunktionsstörung waren präprozedurales Kreatinin ≥ 1,8 mg / dl ($p = 0,022$) und eine verringerte präprozedurale GFR <60 ($p = 0,020$). Mit Ausnahme eines Patienten kehrte die Nierenfunktion bei allen Patienten im Verlauf zum Ausgangswert zurück. Ein Patient (1.3%) verstarb im Beobachtungszeitraum aufgrund einer Lungenarterienembolie (nicht assoziiert mit der Embolisation).

Die selektive interventionell radiologische Embolisation ist bei der Behandlung von Nierenblutungen technisch mit hohem Erfolg machbar, wirksam und gewährleistet in der Regel die Erhaltung des Nierenparenchyms. Die relativ hohe Rate an akuten Nierenfunktionsstörungen ist multifaktoriell zu erklären (Grunderkrankung, vorherige Operation, Embolisationstherapie) und in der Regel reversibel.

Abstract

Renal bleeding is relatively rare but often a potentially life-threatening condition and requires rapid diagnosis and treatment. Most patients are managed with conservative treatment when there is no sign of active bleeding in imaging, but intervention may be needed in up to 7% of cases. Surgical management was the only option traditionally for patients with failed conservative therapy. However, renal artery embolization offers a minimally invasive therapy option, and many case series have shown its efficacy in the emergent management of renal bleeding. However, the comprehensive evaluation of efficacy and long-term safety of renal artery embolization needs to be clarified yet.

We retrospectively identified all the patients who underwent renal artery embolization at our hospital for renal bleeding between January 2010 and June 2020. Preprocedural characteristics, technical details, clinical outcomes, and complications were documented.

A total of 76 patients with a mean age of 67.3 years underwent 86 procedures. The most common etiology was iatrogenic bleeding with 63 patients, and 44 of them had bleeding after partial nephrectomy. Bleeding was successfully controlled at the end of 80 procedures, and the technical success rate was 92.8 %. Clinical success, defined as control of bleeding with endovascular embolization, was achieved in 72 of 76 patients (94.7 %) with embolization, including seven patients who needed re-intervention. Risk factors for clinical failure were antiplatelet agents ($p = 0.033$) and technical failure ($p < 0.001$). Multivariable analysis identified the technical failure as the only significant risk factor, while antiplatelet agents were marginally non-significant ($p=0.051$). Only one patient (1.3 %) underwent nephrectomy due to bleeding. Acute kidney injury (≥ 0.3 mg/dL increase in creatinine within two days) was seen after 16 (21 %) procedures, and risk factors for acute kidney injury were preprocedural creatinine ≥1.8 mg/dL ($p = 0.022$) and decreased GFR <60 ($p = 0.020$). There was no significant correlation with acute kidney injury and procedural characteristics. Except for one patient, the renal function returned to baseline in all patients. One (1.3%) patient was lost due to pulmonary embolism.

In conclusion, renal artery embolization is feasible, safe, and effective in the treatment of renal bleeding. It offers preservation of renal parenchyma, and despite the considerable risk of acute kidney injury, deterioration of renal function is reversible in most cases.

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AKI	Acute kidney injury
AV	Arteriovenous
AVP	Amplatzer vascular plug
CT	Computed tomography
eGFR	estimated Glomerular filtration rate
EVOH	Ethylen-Vinylalcohol-Copolymer
F	French
FAST	Focused assessment with sonography for trauma
Hb	Hemoglobin
L	Lumbar
MVP	Microvascular plug
PA	Pseudoaneurysm
RCC	Renal cell carcinoma
US	Ultrasound

1. Introduction

1.1 Renal artery embolization

Renal artery embolization is the complete or partial occlusion of the renal artery or its branches using various types of embolic materials. This occlusion can be at the large vessels (proximal embolization) or at the capillary level (distal embolization) depending on the indication of the procedure and temporary or permanent depending on the type of the agents used. The procedure has been described in the early 1970s using autologous clots (1, 2), and since then, it has been tremendous developments in embolic materials, as well as catheter technology. Renal artery embolization has been utilized in various clinical scenarios as a minimally invasive treatment option, including treatment of benign renal tumors (e.g., angiomyolipoma) (3), palliation or presurgical devascularization of renal cell carcinomas (4), medical renal diseases (e.g., proteinuria) (5), and emergent procedures for the treatment of renal bleeding due to trauma, surgery, aneurysms, vascular malformations, or renal malignancies (6-10). Although the technical considerations are similar, emergent procedures for renal bleeding requires special attention due to unique challenges related to the general situation of the patient (e.g., hypotension), loss of renal parenchyma due to the event leading to bleeding (e.g., trauma or surgery), and need for rapid resolution of the vascular pathology.

1.2 Renal artery bleeding

Renal artery bleeding is a relatively rare but life-threatening condition requiring rapid recognition and management. Kidneys are highly vascular organs receiving 25% of the cardiac output at each cycle. The leading causes of renal artery bleeding are blunt or penetrant trauma; iatrogenic procedures, such as biopsy, percutaneous drainage or ablation, and surgery; anticoagulation; and spontaneous (Wunderlich syndrome) due to underlying neoplastic and nonneoplastic renal pathologies, including renal angiomyolipoma and renal cell carcinoma (11-14).

The kidneys are the most commonly injured urologic organ in patients with abdominal trauma, with an overall incidence of 1.2-3.25% (15, 16). Although blunt renal trauma is much more common than penetrating trauma, the risk of arterial injury is higher after penetrating trauma (17). However, the most common etiology of renal bleeding in the clinical routine is iatrogenic and secondary to renal biopsy, percutaneous procedures, or surgery. Although these procedures have a low rate of hemorrhagic complications, their increased utilization results in a high incidence of renal bleeding. The risk of significant bleeding after a percutaneous biopsy has been reported around 2.2%, which increased up to 3.4% in case of emergent cases (18). In patients with renal cell carcinoma, partial nephrectomy has replaced radical nephrectomy in most situations. Although it is associated with lower overall complications, hemorrhagic complications are more common following partial resection (19). Another systematic review has shown that the risk of renal artery pseudoaneurysm is two times more common after partial nephrectomy (20). Furthermore, increased usage of anticoagulant and antiaggregant agents is associated not only with the risk of spontaneous bleeding, it also caused an increase in the incidence of postprocedural bleeding (21). In patients with chronic anticoagulation, the rate of transfusion needs after renal-adrenal surgery increased to 24% and the rate of postoperative bleeding to 8%, compared to patients without anticoagulation from 5.2% and 0.9%, respectively (22).

1.2.1 Renal arterial anatomy

The renal arteries arise from the anterolateral aspect of the abdominal aorta at the level of L1-L2. At the level of the renal hilum, the main renal artery divides into an anterior and a posterior branch, which receive 75 and 25% of the renal blood flow, respectively. As a variant, the main renal artery can branch into segmental arteries more proximally to the hilum, which is called early division. Each branch gives segmental arteries, which bifurcate into lobar arteries penetrating renal parenchyma before dividing into the inter-lobar arteries. The interlobar arteries give rise to the arcuate arteries and then interlobular arteries, which become the afferent arterioles of the glomeruli.

In up to 30% of the patients, multiple renal arteries can be seen, and they are named according to the location where they enter the kidney. While accessory renal arteries enter the kidney from the hilum like main renal arteries, aberrant renal arteries puncture the renal capsule outside the hilum. These renal arteries usually arise from the aorta or iliac arteries, but rarely the origin from the thoracal aorta, mesenteric, and lumber arteries have been reported.

1.2.2 Diagnosis of renal bleeding

Patients with renal hemorrhage may present with a wide range of symptoms from non-specific discomfort to hypovolemic shock. Most common indications for further evaluation are acute abdominal or flank pain, decrease in hemoglobin, hematuria, or bloody in drainage. Ultrasound offers the advantage of portability and widespread availability,

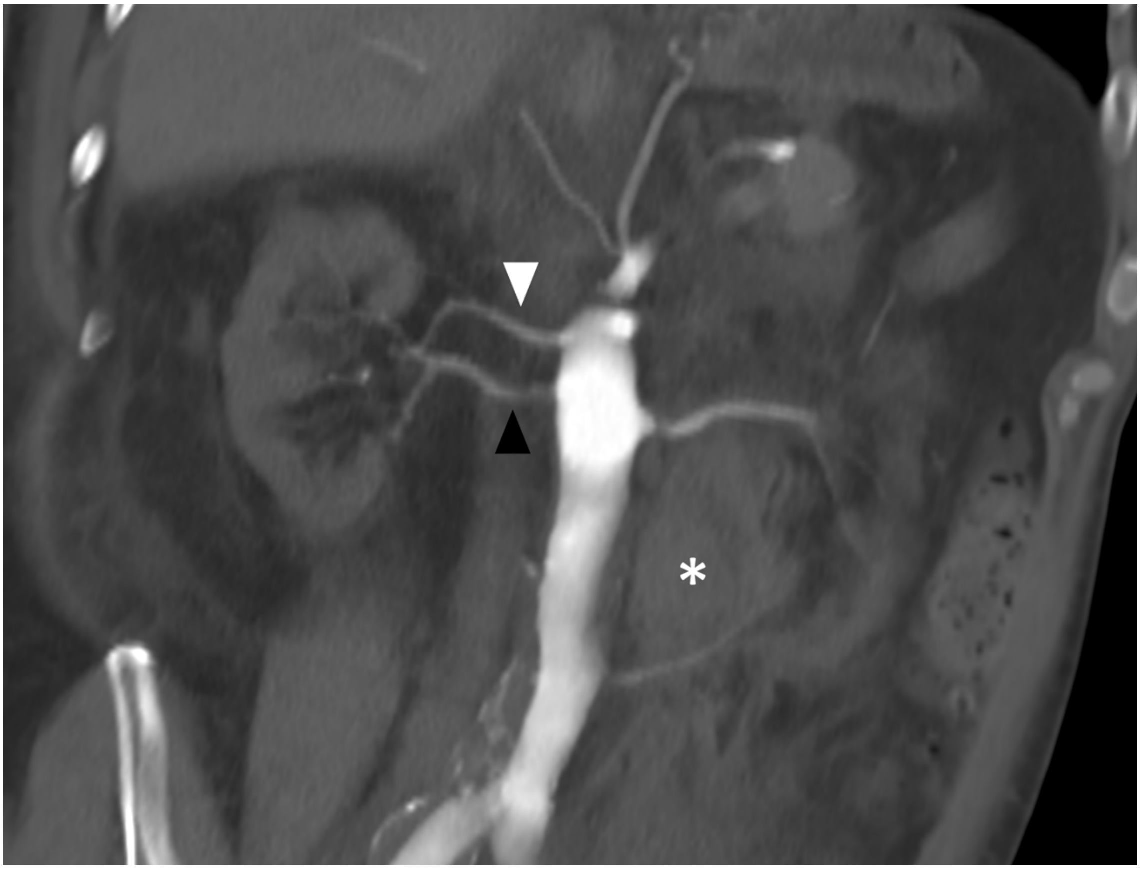


Figure 1.1. Accessory renal artery

In a patient with retroperitoneal hematoma (asterisk) following biopsy of the left kidney, CT angiography shows accessory right renal artery (white arrowhead) entering the kidney at the hilum alongside the right main renal artery (black arrowhead).

and a focused assessment with sonography for trauma (FAST) is commonly performed in emergency departments. Although ultrasound can identify hematoma or vascular pathologies such as pseudoaneurysm and arteriovenous malformation, it is limited in depicting active extravasation, details of arterial anatomy.

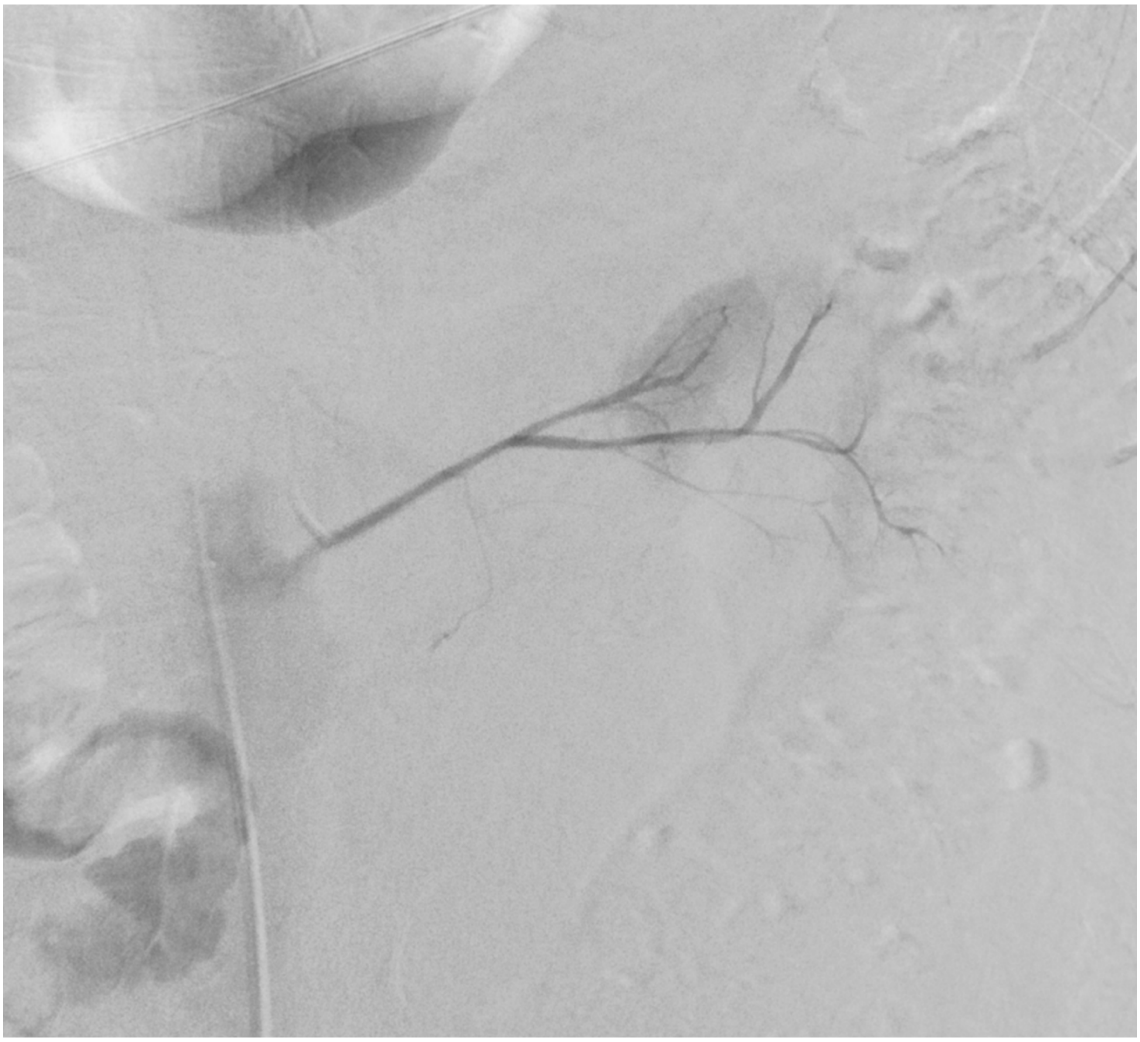


Figure 1.2. Aberrant renal artery

DSA image shows left aberrant renal artery entering kidney outside the hilum and supplies upper pole of the kidney.

Additionally, due to low sensitivity to detect retroperitoneal pathology, a negative ultrasound does not exclude the presence of renal injury (23), especially in obese or clinically instable patients. In selected cases, specific US contrast agents can improve diagnostic accuracy (24).

Contrast-enhanced CT and CT angiography are the primary imaging tools in the diagnosis of renal hemorrhage. CT protocol for the investigation of bleeding requires multiphasic imaging, including pre-contrast followed by arterial and venous imaging after the injection of iodinated contrast material. In patients with suspected collecting system injury, delayed phase images can be obtained. CT helps to identify parenchymal and vascular damage, vascular anatomy, the origin of bleeding and accompanying injuries. Previous studies have shown a good correlation between findings in CT and catheter angiography (10, 25) and very high detection of vascular injury in CT angiography (9).

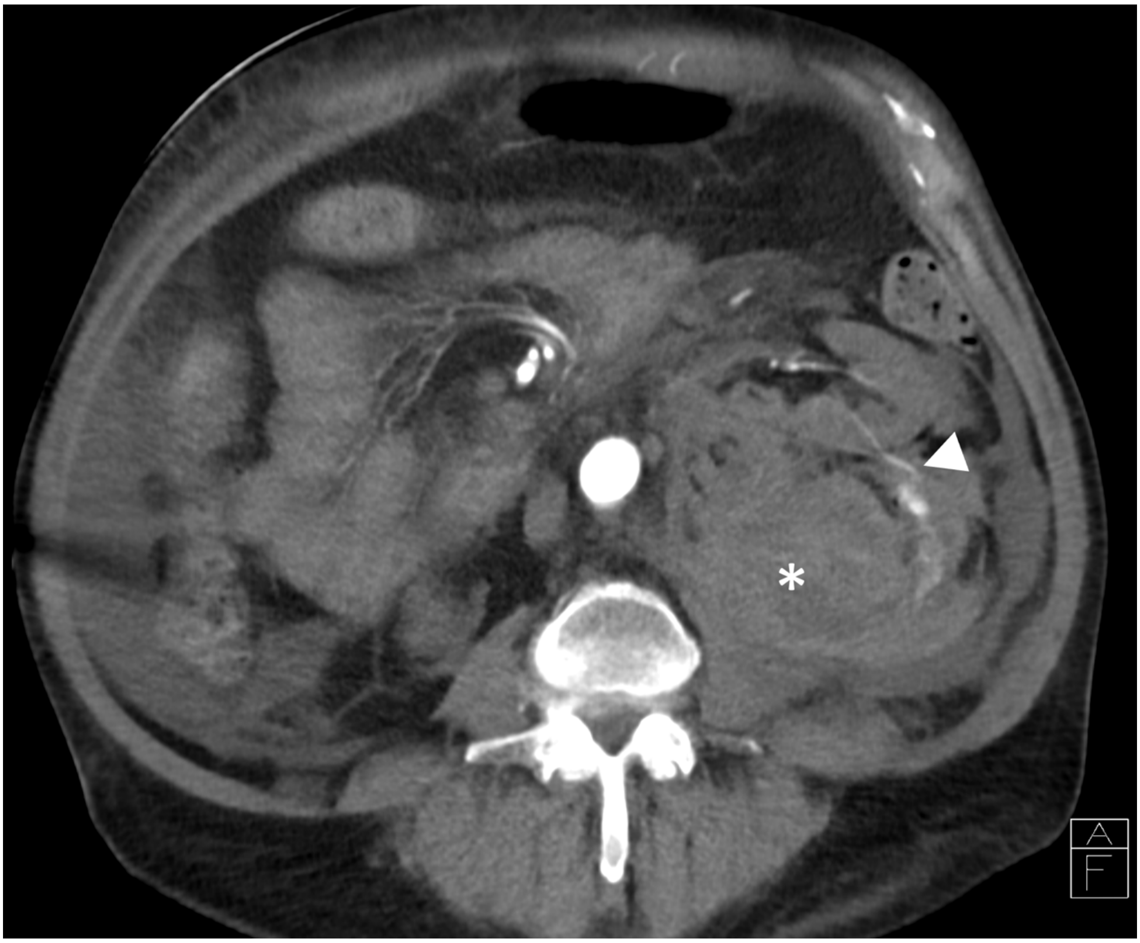
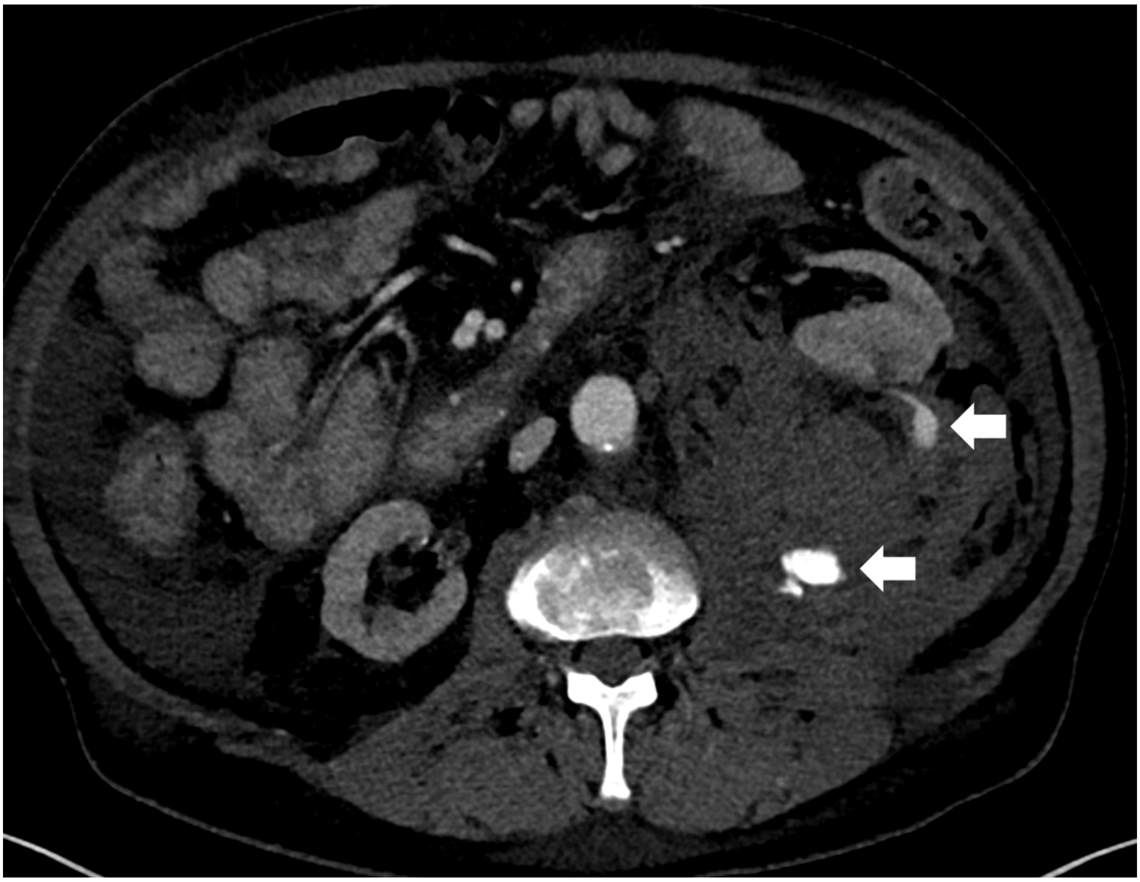


Figure 1.3. Active contrast extravasation in CT

Axial CT angiography shows active contrast extravasation from lower pole of left kidney in the arterial phase (arrowhead in upper image) which further accumulates in the venous phase (arrows in lower image). Asterisk shows retroperitoneal hematoma.



Catheter angiography was traditionally the primary imaging tool in depicting renal arterial injury, but now it is very rarely used for diagnostic purposes and a part of endovascular treatment. Similarly due to increased use and widespread availability of CT substantially reduced the need for diagnostic laparotomy.

1.2.3 Treatment

The main goal of the treatment of renal bleeding is to minimize hemorrhage while preserving the renal function. The combination of the findings on CT with the clinical status of the patient helps to define the optimal management strategy. Conservative treatment is usually sufficient in patients with perirenal hematoma without signs of active bleeding in CT. However, up to 7% of patients with any grade of renal bleeding require further interventions. Although surgical treatment can still be needed in some patients, selective transcatheter embolization became the first choice in most centers in patients after failed conservative treatment due to its minimally invasive nature.

1.2.3.1 Conservative therapy

Conservative therapy includes in-hospital observation with supportive care, including fluid resuscitation, pain management, repeated laboratory follow-ups. The most important laboratory parameters to follow are hemoglobin and creatinine. In case of deterioration in the clinical status repeating imaging can be necessary.

Non-operative management has been shown to suffice in most patients with minor renal injury (26). In patients with parenchymal laceration but no arterial injury, many physicians prefer a conservative approach as long as the patient is hemodynamically stable (27). Retrospective surveys showed that after initial clinical and imaging assessment, non-operative management was preferred in 84-95% of the patients with traumatic renal injury without active bleeding. However, in 2.7-5.4% of the conservatively managed patients, further interventions were needed due to re-bleeding (28, 29).

1.2.3.2 Surgery

Although surgical exploration traditionally was the routine in most cases, now it is performed rarely in selected cases with severe hemodynamic instability, concomitant severely injured intraabdominal organs, urine leaks, or involvement of more than 50% of the kidney. The surgical approach is transperitoneal in most cases to isolate renal artery and vein before exploring the kidney. Previous studies showed that this approach reduced the need for nephrectomy significantly (30).

Additionally, in patients with main renal artery or vein injury, surgical treatment is often necessary. However, results of surgical revascularization of the renal artery are disappointing. In a study reporting outcomes of the patients with renal injury, only of the nine patients who underwent surgical repair achieved complete renal preservation (31).

Furthermore, surgical management is associated with some other risks. Following trauma, in up to 30% of the cases, surgical management results in radical nephrectomy (32). Additionally, during emergency laparotomy in patients with other intraabdominal organ injuries, renal injuries might be overlooked unless clinically suspected or confirmed by pre-surgical imaging. In patients with post-surgical bleeding, further surgeries are associated with the risk related to adhesions. Also, in patients with biopsy-related bleeding, surgical evaluation of a narrow-wound tract is limited due to inadequate visibility.

1.2.3.3 Transcatheter embolization

Transcatheter embolization should be preferred over surgical management in hemodynamically stable patients without concomitant intraabdominal organ injury necessitating surgery. Additionally, rapid angiographic evaluation and embolization could stabilize the patient and recover the hemorrhagic shock which preclude the need for further surgeries. Furthermore, previous studies have reported cases with successful embolization following failed surgical attempts in inappropriate surgical candidates, such as patients with narrow tract injuries.

The main selection criteria for embolization are dropping hematocrit, persistent hematuria, presence of arterial injury findings on imaging, such as pseudoaneurysm, arteriovenous fistula, and active extravasation, or presence enlarging hematoma on serial images. Although ideal candidate for angiography should be hemodynamically stable, in patients with hemorrhagic shock, considering it could provide rapid control of bleeding and stabilization of the patient, angiography could still be preferred over surgery (33).

1.3 Technical considerations for renal artery embolization

To preserve as much as possible renal parenchyma, partial embolization of the kidney by elimination of only the pathological vessels is preferred in appropriate cases. This is done by selective catheterization and embolization of segmental or lobar renal artery branches that supply the pathology. Alternatively, when possible, superselective embolization of more distal branches can be done. However, complete devascularization of the kidney may be needed in some cases, such as complete or near-complete replacement of renal parenchyma with tumor. In those cases, the catheter is positioned to the proximal main renal artery, and a proximal embolization is done.

Based on the location of embolization and expectations from the procedure, several agents can be used. Temporary embolic agents, like gelation sponge, are usually preferred to devascularize tumors before surgery, but they also can be used as a hemostatic agent. Gelatin sponge is preferred due to its low cost and biodegradability; however, the unpredictability of the final distribution and duration of vascular occlusion limits its usage. Gelatin sponge is also available in the market as a powder with an approximate diameter of 40-60 µm, which can be used to obtain distal embolization.

Inert microparticles provide permanent distal occlusion of the vascular bed, and calibrated different sizes are available in the market, offering an opportunity to choose the level of occlusion. They are diluted in contrast agent and saline solution, which provides radio-opacity to control embolization speed and avoid non-target injection. Microparticles are preferred in most cases with distal occlusion, like tumors.

Metallic coils are available in the market in different sizes from submillimeter to several centimeters, and various configurations such as straight, helical, spiral, and three-dimensional shapes. They are inserted through the various size of catheters, including micro-catheters. Besides thrombogenic coating, fibered coils with tiny fibers attached to the metal component are available to increase thrombogenicity. Although pushable coils are preferred primarily due to low cost, detachable coils which offer repositioning can be used in case of high-risk for non-target embolization, like high flow arteriovenous fistulas (34).

Figure 1.4. Coil embolization of active extravasation

Right renal angiogram shows active contrast extravasation from the lower pole in a patient underwent partial nephrectomy (arrow). Control angiogram following embolization (lower image) with pushable coils (arrowheads) showed cessation of bleeding and lack non-target embolization with maintained renal perfusion.

Detachable vascular plugs (Amplatzer vascular plug [AVP], St. Jude Medical Inc., USA or Microvascular plug [MVP], Medtronic, USA) provide rapid embolization of larger vessels (≥1,5mm) and preferred in high-flow vascular pathologies, especially in AV fistulas with risk for migration of the embolic material. The main limitation of vascular plugs is decreased navigability and the need for large bore catheters to deploy due to large size, especially in AVP (35).

Cyanoacrylates (glue) are the most commonly used liquid embolic agent in renal artery embolization. It provides vessel occlusion by polymerization upon contact with the blood. Glues are diluted with high viscosity iodized oil (Lipiodol, Guerbet, France), which provides radio-opacity and determines polymerization speed. Glue embolization has demonstrated high success in permanent distal occlusion; however, they require experience and must be used cautiously to avoid non-target embolization. New non-adhesive liquid embolics compose of ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulphoxide mixed with micronized tantalum powder for visibility under fluoroscopy. After contact with blood, EVOH precipitates and forms a cast that remains flexible for about 5 minutes, allowing to slowly build up a cast into the vessels. Despite better control of embolization with EVOH than glue, it is rarely used in bleeding due to its high cost.

Although there are reports for utilization of other embolic agents like detachable balloons, they are rarely used in renal artery embolization.

1.4 Complications of renal artery embolization

Previous case series have shown that renal artery embolization is a safe procedure with relatively low rates of complications with 5-6% due to the minimal invasive nature of the procedure (9, 10, 36, 37). Complications related to the endovascular maneuvers, such as problems related to vascular access or arterial dissection, can be avoided with technical modifications, including ultrasound-guided puncture and using vascular closure devices for hemostasis. Postembolization syndrome can be seen up to 44% of the patients, especially in patients with a large volume of renal infarction; however, it is usually asymptomatic, self-limiting and managed conservatively (38, 39). Contrast-induced nephropathy or allergic reactions can be seen due to iodinated contrast injections. Although contrast-induced nephropathy is mostly transient, due to concomitant loss of renal tissue after renal artery embolization, permanent deterioration in kidney function can be seen (40).

With the advancement in catheter technology and improvements in embolic agents, non-target embolization to the spine, lower extremity, bowel, or adrenal glands is extremely rare nowadays. Inappropriate embolic agents can result in migration, especially in patients with high-flow arteriovenous fistulas. Coil migration has been reported in around 2% of cases (8). The tip of the catheter can remain in the glue cast and may result in the inability to remove the catheter (41). Large volumes of ischemic kidney can cause infectious complications necessitating percutaneous drainage (42). Additionally, worsening in blood pressure control has been reported up to a rate of 32% following renal artery embolization (43).

1.5 Aim of the study

Although renal artery embolization has become an effective therapeutic option in many urologic conditions, literature mostly consists of case reports and case series and lacks a detailed evaluation of the procedure. Additionally, there has been improvements in catheter and embolic agent technology, and results of new techniques need to be evaluated. Furthermore, in most studies, elective and acute embolization procedures have been analyzed together, although the aim and expected outcomes differ.

This study aimed to evaluate the technical success of transcatheter embolization in patients with acute renal bleeding, the clinical outcome of the procedures, the effect of embolization on renal function, and identify factors for treatment failure and complications.

2. Materials and Methods

2.1 Study design

The electronic database of the hospital was searched for all patients who underwent renal angiography, and patients referred for a suspect of or known renal artery bleeding were identified. Patients with no sign of active bleeding and a diagnosis of angiomyolipoma were excluded. Pretreatment characteristics of all patients were recorded, including age, gender, primary diagnosis, bleeding etiology, history of chronic kidney disease, antiplatelet or anticoagulation treatments, preprocedural renal function tests. In patients with bleeding after surgery, surgical approach and technique, and when presurgical images available, RENAL scores (**R**adius [maximum diameter], **E**xophytic/endophytic tumor location, **N**earness to the renal collecting system or renal sinus [mm], **A**nterior or posterior location, and **L**ocation relative to the renal poles) were recorded.

The definition of technical success was the complete control of bleeding or the control/therapy of the vascular pathology (i.e., pseudoaneurysm or arteriovenous fistula) at the end of the embolization procedure. The clinical success of embolization was defined as no further bleeding or additional procedures related to hemorrhage within one month following embolization. Procedure characteristics, including angiographic findings, embolic agents, iodinated contrast agent dose, and the number of embolized branches, were collected via the electronic database and evaluation of procedural angiograms. Selective embolization was defined as pre-serving the main renal artery, and superselective embolization as a maximum of one segmental or three subsegmental renal arteries. Postprocedural medical records were evaluated, and follow-up hemoglobin, serum creatinine, and eGFR results were collected.

2.1.1 Embolization technique

In our center, transcatheter embolization procedures are usually done under local anesthesia; however, general anesthesia may be needed in clinically unstable patients. Although minor technical differences between operators, embolization is made as follows: After sterile preparation, arterial access is achieved with placement of a 5F vascular introducer into the right or left common femoral artery. The renal arteries are catheterized with a selective angiography catheter (Cobra or Simmons 1), and angiographies are obtained to visualize the arterial anatomy with an injection of 10 cc contrast material. Following identification of the vascular pathology, a microcatheter is advanced to the target vessel. Contrast injections are repeated to confirm catheterization of target artery, and embolization is performed using several embolic agents, such as coils, particles, vascular plugs, stent-grafts. Coils are preferred in all feasible cases, and in all procedures with coiling, fibered coils are used. Although pushable fibered coils (Cook Medical Inc., Bloomington, Indiana, USA) are used mostly, detachable coils are selected in patients with pseudoaneurysm supplied by a short-necked branch or with high-flow arteriovenous fistula creating risk for coil migration. In case of further involved branches, similar steps are repeated for all injured vessels. Before removal of the material, control of bleeding or no residual flow to the vascular pathology is confirmed with angiograms. An extravascular mechanical closure device (Mynxgrip [Mynx], Cordis, USA) is used to obtain hemostasis, and a pressure bandage is applied for 24 hours.

2.1.2 Statistical analysis

All statistical analyses were performed using SPPS version 23.0 (IBM, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation. Categorical variables were compared using Chi-Square and Fisher’s exact tests to identify the association of baseline and procedural characteristics with technical or clinical failure and postprocedural acute kidney injury. Variables with a p value <0.5 in the univariate analyses were included in the multivariable analysis. Binary logistic regression was used to identify independent predictors of clinical failure. Additionally, paired t-test was used to analyze periprocedural changes in renal function parameters and hemoglobin values.

3. Results

3.1 Baseline characteristics

3.1.1 Study population

Seventy-six patients underwent a total of 86 procedures. 60 (78.9%) of the patients were male, and the mean age of the study population was 67.3±12.9 (24-92 y). Iatrogenic procedures were the leading cause of renal hemorrhage (63/76, 82.8%), followed by bleeding from the tumor (7/76, 9.2%), trauma (3/76, 3.9%), and spontaneous bleeding (3/76, 3.9%).

In patients with iatrogenic bleeding, underlying etiology were surgical operation in 48, percutaneous biopsy in 9, anticoagulation in two patients, and double-J-stent placement with percutaneous renal access, inadvertent wire injury in coronary angiography, imaging guided percutaneous drainage, and local ablation each in one patient.

Twenty-nine (38.2%) patients had a history of chronic kidney disease. In four patients, bleeding occurred in a transplanted kidney. One patient with kidney transplantation had spontaneous bleeding of the native kidney. Two patients had a solitary kidney, one presented with bleeding after partial nephrectomy for RCC, and the other had spontaneous bleeding from RCC. Forty-four (57.9%) patients were receiving combined or alone anticoagulation/antiplatelet therapy at the time of bleeding.

Table 1. Baseline characteristics

	N=76
Age (mean, range)	67.3, 24-92
Gender	
• Male	60 (78.9%)
• Female	16 (21.1%)
Bleeding Etiology	
Iatrogenic	63 (82.8%)
• Surgery	48
• Biopsy	9
• Anticoagulation	2
• Percutaneous interventions	4
Tumor	7 (9.2%)
Trauma	3 (3.9%)
Spontaneous	3 (2.7%)

The most common symptoms of the patients were macrohematuria (40 patients), followed by a decrease in hemoglobin (13), pain (12), blood in drainages (2), fever (1), fever and increase in creatinine (1), increased creatinine (1), and syncope (1). Sixty-three (82.8%) patients underwent non-invasive imaging with ultrasound or CT before the angiography. Four patients had history of reoperation due to bleeding after initial surgery (two patients on the same day, one patient after 1, another after 5 days). In patients with a history of invasive procedures such as surgery or biopsy, the median time between the initial procedure and the onset of renal bleeding was ten days (range, 0-92).

3.1.2 Surgical details

In patients who had bleeding after surgery, 44 patients (39 male) underwent partial nephrectomy (38 had RCC and 6 had oncocytoma). The surgical approach was open in 38 cases (22 patients with lumbar, 16 patients with abdominal approach), robot-assisted (DaVinci) in five cases, and retroperitoneal laparoscopy in one case. One of the patients undergoing open abdominal surgery received bilateral partial nephrectomy due to bilateral renal cell carcinoma. In patients with renal resection, preoperative images for evaluation of RENAL score were available in 31 patients. The mean RENAL score was 9.1±2.4 (range, 4-12), and patients with an open approach had a higher renal score than patients who underwent minimally invasive surgery (9.8 vs. 5.6, p=0.007). Other surgical procedures were percutaneous nephrolithotomy in 3 patients and renal artery bypass surgery due to renal artery stenosis in one patient.

Table 2. **Surgical procedures**

	N=48
Partial nephrectomy	44
• Open lumbar	22
• Open abdominal	16
• Robot-assisted	5
• Retroperitoneal laparoscopy	1
Percutaneous nephrolithotomy	3
Renal artery by-pass	1

3.2 Procedural outcome

3.2.1 Technical success

At the end of the procedure, control angiography showed cessation of the bleeding or complete exclusion of the vascular pathology (pseudoaneurysm, arteriovenous fistula) in 71 of 76 cases. In one further patient, control sonography revealed a spontaneous occlusion of a small residual perfusion of a pseudoaneurysm two days after the procedure. The other four patients underwent a second embolization procedure. One patient with a large arteriovenous fistula was referred to surgical correction due to the high risk of material migration with non-target embolization resulting in ischemic complications. The patient had rebleeding three days after the surgery, and CT revealed residual arteriovenous fistula, which was treated with coil embolization. After embolization of a large pseudoaneurysm with coils and particles, a small residual pseudoaneurysm was left for the follow-up to sustain enough viable kidney tissue in another patient. Due to persistence in serial Doppler examinations, the residual pseudoaneurysm was embolized with coils four days after the initial procedure. In one patient with bleeding from metastatic RCC with renal vein invasion involving mostly the lower pole of the kidney, lower pole branches were selectively embolized with particles followed by coiling of the segmental branches to preserve healthy kidney tissue in the upper pole. Due to rebleeding, the rest of the kidney was embolized with particles, and the main renal artery was occluded with coils 15 days later. Another patient with a pseudoaneurysm of a small branch had a dissection of the segmental branch supplying the pseudoaneurysm during catheterization, and control angiographies revealed no filling. Six days later, the patient underwent another angiography due to a drop in hemoglobin, but catheterization of the branch supplying the pseudoaneurysm failed, and the patient was treated surgically. Table 3 shows the results of univariable analysis to identify factors associated with technical failure.

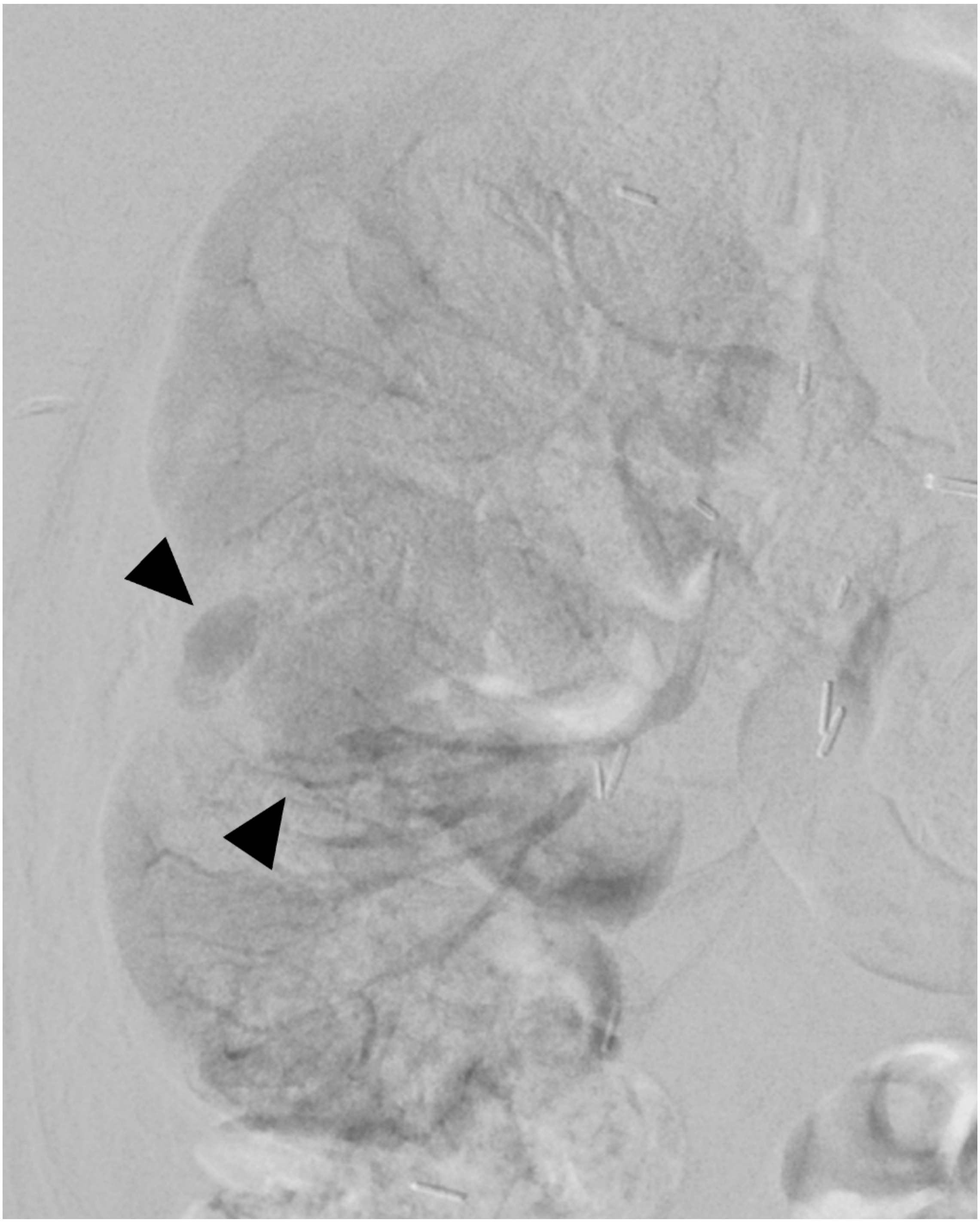


Figure 3.1. Coil embolization of pseudoaneurysm

A 71-years old patient presented with right flank pain 9 days after partial nephrectomy due to renal cell carcinoma. CT images showed pseudoaneurysm (not shown) and embolization was planned. Right renal angiogram (upper image) showed two pseudoaneurysms (arrowheads) at the middle portion of the kidney. Control angiogram following coil embolization (lower image) showed no residual filling in pseudoaneurysms.

Table 3. Factors associated with technical success

Variable	Technical success		
n=86	yes	no	p value
Age (>65 years)	62.5% (50/80)	66.7% (4/6)	0.604
Gender (male)	77.5% (62/80)	83.3% (5/6)	0.603
Chronic kidney disease (yes)	40% (32/80)	33.3% (2/6)	0.554
Antiplatelet	33.8% (27/80)	50% (3/6)	0.347
Anticoagulation	35% (28/80)	33.3% (2/6)	0.653
Antiplatelet or coagulation	58.8% (47/80)	83.3% (5/6)	0.231
Selective embolization (n=83)	88.8 (71/80)	100% (3/3)	0.706
Hb >7 g/dL	91.3% (73/80)	6.4% (5/6)	0.454
Creatinine ≥1.8 mg/dL	36.3% (29/80)	50% (3/6)	0.396
eGFR <60 mL/min/1.73 m^2	21.3% (17/80)	0% (0/6)	0.255
Contrast dose ≥150 ml	83.8% (67/80)	50% (3/6)	0.075

Besides the four patients mentioned above, six patients underwent a second embolization procedure. A patient with extensive RCC underwent a successful embolization of the main renal artery with particles and coils. Six months after the initial procedure, the patient had a rebleeding from the aberrant lower pole artery, and this branch was embolized with coils. Five more patients presented with a rebleeding after technically successful embolization (median three days after the initial procedure, range 1-21 days) and were treated endovascularly. Two patients presented with a rebleeding requiring treatment: one patient with urothelial carcinoma, who underwent non-selective embolization of the renal artery with particles and coils, had bleeding due to a fistula between the common iliac artery and ureter and was treated with a stent-graft. Another patient who needed anticoagulation due to total aortic arch replacement surgery due to Marfan syndrome-related aortic dissection had a rebleeding three days after the embolization and underwent radical nephrectomy.

Table 4. Details of procedures with technical failure

ID	Age / Gender	Vascular pathology	Embolic agents	Reason for failure	Outcome	Rebleeding
4	60 / Male	PA	coils & particles	Small PA was left to limit embolization of healthy kidney	Underwent second emboli-zation due to persistence in follow-up imaging (success-ful)	No
52	61 / Female	AVF	---	No embolization was performed due to high risk of material migration	See table 5	Yes
53	79 / Male	PA	---	Due to dissection of the segmental branch PA could not be catheterized	See table 5	Yes
55	74/ Male	PA & AVF	coils	Small PA with slow flow decided to be followed to limit embolization of healthy kidney	Spontaneous thrombosis two days after the procedure	No
64	80 / Male	Tumor blush	coils	Small branches supply-ing tumor was not embo-lized to save tumor-free upper pole of the kidney	See table 5	Yes

AVF: arteriovenous fistula, PA: pseudoaneurysm

Mean contrast medium dose per procedure was 99±48.4 ml (range, 20-260). In three procedures, no embolization was done after diagnostic angiography (see table 4). The most common used embolic agent was coils (Table 6).

Table 5. Additional procedure details

	ID	Disease	Bleeding etiology	Preprocedural Anticoagulation	Reason for additional procedure	Embolization material	Outcome	Rebleeding
Endovascular renal procedures	4	RCC	Surgery	Enoxaparin	Technical failure / PA in control US	Coils	Successful selective embolization	No
	9	RCC	Surgery	ASA	Rebleeding	Coils	Successful selective embolization	No
	12	RCC	Surgery	ASA + Heparin	Rebleeding	Coils	Successful selective embolization	No
	21	RCC	Local ablation	Apixaban	Rebleeding	Coils	Successful selective embolization	No
	29	RCC	Tumor	Clopidogrel	Rebleeding	Particles	Successful non-selective emboliza-tion	No
	42	RCC	Tumor	---	Rebleeding from accessory renal artery	Coils	Successful non-selective emboliza-tion	No
	52	RCC	Surgery	---	Initial procedure with technical failure. Rebleeding after surgi-cal correction AVF	Coils	Successful selective embolization	No
	53	RCC	Surgery	ASA + Clopidogrel	Technical failure / rebleeding	---	Unsuccessful second procedure due to failed catheterization of the branch.	Yes (Underwent surgery)
	56	RCC	Surgery	ASA + Heparin	Rebleeding	Coils	Successful selective embolization	Yes (sponta-neous resolu-tion)
	64	RCC	Tumor	Apixaban	Technical failure / rebleeding	Coils + particles	Successful non-selective emboliza-tion	No
Other	45	RCC	Surgery	Marcumar	Rebleeding	---	Radical nephrectomy	No
	65	Urothelial carcinoma	Tumor	no	Fistula between com-mon iliac artery and ureter	---	Stent-graft placement	No

ASA: Acetylsalicylic acid, RCC: Renal cell carcinoma

Overall technical success was 93% (80 of 86 procedures), and in linear regression analysis, risk factors such as a hemoglobin level ≤ 7, age, gender, chronic kidney disease, anticoagulation, antiplatelet therapy, pre-interventional creatinine, the time between surgery and bleeding (≤30 vs. >30 days), bleeding etiology or surgical technique were not significantly associated with technical failure of the embolization procedure (see table 3).

3.2.2 Procedural complications

Intraprocedural coil migration was encountered in one procedure: in a patient with a high flow arteriovenous fistula, a coil migrated to venous circulation and stuck in the right atrium, patient is asymptomatic. In another patient, a dissection of a subsegmental branch supplying the pseudoaneurysm occurred in one patient, and catheterization failed (see above). The patient had rebleeding and underwent a second procedure, which is also unsuccessful due to failed catheterization of the branch. The patient underwent surgical treatment. The overall procedural complication rate was 2.3 % (2/86).

Table 6. Embolization material

Embolic agents used	**Number of procedures**
Microcoils alone	68
Microcoils & particles	8
Stent-graft	3
Vascular plug & coils	2
Vascular plug & particles	1
Particles	1
No embolization	3

3.2.3 Clinical success

Clinical success was achieved in 72 of 76 patients (94.7%) undergoing embolization, including seven patients with two embolization procedures. Univariate analysis revealed that the use of antiplatelet agents ($p=0.033$) and procedures with technical failure ($p<0.001$) were risk factors for clinical failure. Multivariate analysis showed that technical failure was the only independent risk factor ($p=0.001$), and the usage of an antiplatelet agent was marginally non-significant ($p=0.051$).

In the partial nephrectomy group, 44 patients had a total of 50 procedures, and clinical success was achieved in 42 patients, including four patients after two procedures. The usage of an antiplatelet agent ($p=0.030$), technical failure ($p=0.002$), and Hb lower than 7 ($p=0.016$) were significant risk factors for clinical failure in univariate analysis, but only the technical failure ($p=0.019$) remained significant after multivariate analysis.

Only one patient needed a radical nephrectomy, and one patient with bleeding from the native kidney after transplantation underwent bilateral prophylactic nephrectomy. Seven patients (9.2%) underwent non-selective embolization of the kidney. In six of these cases, the contralateral kidney was healthy, and the other patient had a transplanted kidney. Six of them had bleeding due to tumors infiltrating most of the kidney and the other patient bleeding from the native kidney after transplantation.

Hemoglobin increased significantly after the intervention (9.3±1.7 vs. 10.3±1.7, $p<0.001$). No cases of mortality due to hemorrhagic complications were encountered. One patient died due to pulmonary thromboembolism six days after the procedure, and the overall in-hospital mortality rate was 1.3%.

Table 7. Factors associated with clinical success

Variable	Clinical success		
n=86	Yes	No	p value
Age (>65 years)	61.6% (45/73)	69.2% (9/13)	0.425
Gender (male)	79.5% (58/73)	69.2% (9/13)	0.311
Chronic kidney disease (yes)	39.7% (29/73)	38.5% (5/13)	0.593
Antiplatelet	30.1% (22/73)	61.5% (8/13)	**0.033**
Anticoagulation	32.9% (24/73)	46.2% (6/13)	0.267
Anti-platelet or coagulation	56.2% (41/73)	84.6% (11/13)	**0.048**
Technical success (yes)	98.6% (72/73)	61.5% (8/13)	**<0.001**
Hb >7 g/dL	93.2% (68/73)	76.9% (10/13)	0.097
Creatinine ≥1.8 mg/dL	37% (27/73)	38.5% (5/13)	0.575
eGFR <60 mL/min/1.73 m^2	79.5% (58/73)	84.6% (11/13)	0.502
Contrast dose ≥150 ml	17.8% (13/73)	23.1% (3/13)	0.452

3.2.4 Renal functions

Creatinine levels measured at discharge were significantly lower than preprocedural levels (2.16±1.76 vs. 1.9±1.5, p=0.002). Similarly, eGFR values increased significantly after embolization (45.7±24.4 vs. 51.7±25.1, p<0.001). Acute kidney injury, defined as an increase of ≥0.3 in creatinine within two days, was seen in 16 (21%) patients after embolization procedures (6/44 in partial nephrectomy group). In all 16 patients, preprocedural eGFR was lower than 60. Eight of these patients already had chronic kidney disease, and all of these patients returned to the baseline stage of chronic kidney disease during the follow-up period (seven at discharge, one after six months). The significant risk factors for AKI were preprocedural creatinine values ≥1.8 mg/dl (p=0.022) and eGFR value lower than 60 (p=0.02). Increased creatinine (≥1.8) and decreased eGFR (<60) were significantly associated with AKI, also in cases with selective embolization (p=0.014 and p=0.012). Neither selective (p=0.883) nor superselective (p=0.876) embolization was associated with AKI.

Except for one patient, who had bleeding after kidney biopsy for the differential diagnosis of acute renal failure, none of the patients had a newly diagnosed chronic kidney disease at discharge. Also, except for the same patient, creatinine values at discharge were lower than preprocedural creatinine values in all patients.

One patient with a history of partial nephrectomy developed hydroureteronephrosis after a bleeding episode, and despite double J stent placement, kidney function deteriorated. Functional imaging three months after the surgery revealed only a 4% function in that kidney, and the patient underwent nephrectomy of the non-functioning kidney, but the creatinine level was already lower than the baseline.

Table 8. Factors associated with acute kidney injury

Variable	Acute kidney injury		
n=86	yes	no	p value
Age (>65 years)	62.5% (10/16)	62.9% (44/70)	0.596
Gender (male)	81.3% (13/16)	77.1% (54/70)	0.507
Chronic kidney disease (yes)	50% (8/16)	37.1% (26/70)	0.251
Antiplatelet	31.3% (5/16)	35.7% (25/70)	0.489
Anticoagulation	37.5% (6/16)	34.3% (24/70)	0.511
Antiplatelet or anticoagulation	68.8% (11/16)	58.6% (41/70)	0.324
Selective embolization (n=83)	93.8% (15/16)	88.1% (59/67)	0.448
Superselective embolization (n=83)	81.2% 13/16	77.6% 52/67	0.983
Technical success (yes)	100% (16/16)	91.4% (64/70)	0.279
Hb >7 g/dL	93.8% (15/16)	90% (63/70)	0.539
Creatinine ≥1.8 mg/dL	62.5% (10/16)	31.4% (22/70)	**0.022**
eGFR <60 mL/min/1.73m^2	100% (16/16)	75.7% (53/70)	**0.020**
Contrast dose ≥150 ml	69.2% (9/13)	83.1% (59/71)	0.210
Clinical success (yes)	93.8% (12/16)	82.9% (58/70)	0.250

4. Discussion

Renal bleeding can be seen due to trauma, anticoagulation, tumors, or iatrogenic procedures, including minimally invasive or open kidney surgery and percutaneous biopsy or drainages. Recent advances in sur- surgical techniques have changed management guidelines for localized renal tumors in favor of partial nephrectomy procedures instead of radical nephrectomy whenever feasible, even in large, central, and endophytic tumors. The increasing number of partial nephrectomy procedures in patients with challenging tumor locations may translate into more patients with hemorrhagic complications. Similarly, increased use of anticoagulants and the amount of percutaneous kidney-directed procedures have increased the number of patients presenting with renal bleeding. Although the vascular injury is minor and conservative management is sufficient in most cases, intervention may be needed due to life-threatening bleeding in up to 5% of patients (20, 44, 45). In patients requiring intervention to control the bleeding, transarterial embolization is preferred over surgical management in many centers due to the minimally invasive nature of this treatment avoiding risks of major surgery with general anesthesia and the inherent risk of conversion to radical nephrectomy.

4.1 Efficacy of renal artery embolization

In our cohort, embolization was successful in 92.8 % of procedures, and clinical success was achieved in 94.7 % of all patients with transarterial embolization. No risk factors for technical failure were identified. The clinical failure rate was lower than previously reported (21–27 %), possibly due to increased experience and technical improvements (9, 36). The technical failure was the only risk factor for clinical failure in multivariable analysis; however, antiplatelet treatment was marginally non-significant ($p = 0.051$).

Based on this result, we suggest bridging with heparin in patients needing antiplatelets, as other authors (46). Furthermore, despite the lack of statistical difference, patients with hemoglobin <7 g/dL had a higher clinical failure rate (33.3 % vs. 13.3 %, $p = 0.097$). This situation could result from increased vasospasm in patients with a higher blood loss complicating procedure, such as demanding selective catheterization and embolization. Also, in these patients, matching the size of embolic agents to the spasmodic vessels might lead to rebleeding after initial stabilization of hemodynamic status. Vasospasm might also lead to overlooking further bleeding foci. These findings are supported by previous reports that showed increased clinical failure in patients needing inotropes (47), and underlines the importance of early imaging and intervention in cases with suspicion of bleeding.

4.2 Preservation of the kidney

Only one patient (1.3 %) needed a nephrectomy due to rebleeding after transarterial embolization in our cohort. The patient required a nephrectomy, had a history of Marfan-related type A aortic dissection and aortic valve replacement, and was under warfarin treatment. Warfarin was bridged with heparin during the periprocedural period and reinitiated two weeks after surgery, which led to bleeding two days later. Although successful embolization with coils, the patient had rebleeding three days after the procedure, and surgical exploration was decided. During surgical management of rebleeding after embolization, a page kidney situation was seen, and the primary suturing failed due to the coagulation status of the patient.

Compared to a previous review of transcatheter embolization cases, the need for open surgical repair (1.3 % vs. 12 %) or radical nephrectomy (1.3 % vs. 10 %) rate was substantially lower in our cohort (36). We believe the increased experience of interventional radiologists in complex embolization procedures, as well as advancements in the catheter and embolic agent technology, have resulted in the improved success of transcatheter procedures. There was a considerable rate of patients with non-selective embolization in our study (9.2 %); however, those patients had no or very low healthy renal tissue in the embolized kidney due to infiltration by the tumor. Microcoils were used in 93.9 % of the procedures in our cohort, and 81.9 % of the cases were treated exclusively with microcoils. Microcoils offer predictable and accurate embolization of small branches. Although other embolic agents (i.e., glue) can be used in renal artery embolization, proximal embolization with microcoils is safe and adequate to control bleeding due to the end-artery organization renal blood flow.

4.3 Effect on renal function

Although renal artery embolization is a minimally invasive procedure, the need for contrast medium injections and loss of a portion of healthy kidney tissue due to embolization create a risk for deterioration in renal function. Acute kidney injury was seen in 21% of the patients in our study. However, except for one patient, all patients returned to preprocedural renal functions during follow-up. That patient had bleeding due to a biopsy for the differential diagnosis of acute kidney failure. After embolization, kidney functions continued to deteriorate, and the patient developed chronic kidney disease. Nevertheless, we believe this was the result of the underlying disease, and although it is not possible to overrule any potential effect of embolization in worsening renal function, embolization is not a major driving factor.

Besides embolization, hypotension, compression due to hematoma, and anemia due to hemorrhage and nephron loss due to surgical resection leading to vascular injury are also responsible for the deterioration in renal function during the periprocedural period.

Our results showed that long-term preservation of renal function was possible after embolization. In our cohort, two patients were embolized following partial nephrectomy of a solitary kidney; and both patients did not develop chronic kidney disease. Risk factors for AKI were increased preprocedural creatinine (≥1.8 mg/dl) and decreased eGFR (<60).

Interestingly, there was no association between acute kidney injury and level of embolization (non-selective, selective, or super-selective). Furthermore, some of the patients who underwent superselective embolization also developed temporary AKI. However, this result should be interpreted carefully. Non-selective embolization was performed only in patients with none or very little healthy kidney tissue to preserve in the embolization area. Also, in patients who underwent selective embolization, embolized parenchyma might not be contributing to filtration due to functional ischemia caused by steal phenomena related to pseudoaneurysm or arteriovenous fistula, although these nephrons are not permanently damaged.

Considering this situation, together with the high risk of rebleeding in patients with technical failure, suggests that exclusion of all vascular pathologies should be pursued in patients with renal bleeding. Medical history of CKD was not a significant risk factor for postprocedural AKI in our cohort, as in previous studies (37). Unlike previous reports, there was no correlation between injected contrast media volume and acute kidney injury in our cohort. Piasecki et al. showed that injection of more than 150 mL of contrast medium is a significant risk factor for acute kidney injury (48). Despite conflicting results in our cohort, we also recommend the careful use of contrast media.

4.4 Limitations

This study has some limitations. First, this study had a retrospective design, and renal hemorrhage was caused by different etiologies. Retrospective nature precluded the evaluation of some factors that might contribute to the results, such as the blood pressure of the patients before and after the procedures. Second, different embolization techniques were used for selective renal artery branch embolization. However, different techniques and embolic agents resulted from various vascular pathologies, vascular anatomy, and the number of bleeding foci. Nevertheless, this situation represents the daily clinical routine and provides information on renal artery embolization in a wide range of clinical conditions. Also, our study provides a comprehensive evaluation of technical and clinical outcomes in a large cohort of patients who underwent renal artery embolization due to bleeding with an additional focus on kidney functions.

5. Conclusions

Renal artery embolization is safe, feasible, and efficient in patients with acute renal bleeding. Despite the risk of renal injury due to embolization of some healthy kidney tissue and contrast injections, deterioration in renal function is generally transient and without long-term consequences. Technical success with complete control of all vascular pathologies should be pursued to avoid rebleeding. Due to the higher risk for clinical failure in patients needing antiplatelet agents, if possible, antiplatelet agents should be bridged with heparin during perioperative period. Compared to the traditional treatment method with surgery, it is associated with substantially lower nephrectomy need and eliminates the risks related to major surgery and general anesthesia; and renal artery embolization should be preferred in patients with renal bleeding after the failure of conservative management.

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Affidavit

Promotionsbüro
Medizinische Fakultät

Eidesstattliche Versicherung

Ich, Osman Öcal, erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Endovascular Treatment of Renal Bleeding: Technical Success, Clinical Tolerability and Overall Success

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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Munich, 19.09.2022 Osman Öcal

Publikationsliste

Teile dieser Arbeit wurden unter folgendem Titel veröffentlicht:

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