Incidence of Bleeding in 8172 Percutaneous Ultrasound-Guided Intraabdominal Diagnostic and Therapeutic Interventions – Results of the Prospective Multicenter DEGUM Interventional Ultrasound Study (PIUS Study)

Blutungskomplikationen bei 8172 sonografisch gesteuerten diagnostischen und therapeutischen intraabdominellen Punktionen – Ergebnisse der prospektiven DEGUM Interventionsstudie (PIUS-Studie)

Authors

D. Strobel[1], T. Bernatik[2], W. Blank[3], U. Will[4], A. Reichel[4], M. Wüstner[5], V. Keim[6], D. Schacherer[7], A. P. Barreiros[8], G. Kunze[9], D. Nürnberg[10], A. Ignee[11], E. Burmester[12], A. A. Bunk[13], M. Friedrich-Rust[14], E. Froehlich[15], A. Schuler[16], C. Jenssen[17], W. Bohle[18], M. Mauch[19], K. Dirks[20], J. Kaemmer[21], C. Pachmann[22], J. Stock[23], M. Hocke[24], A. Kendel[25], C. Schmidt[26], C. Jakobeit[27], H. Kinkel[28], W. Heinz[29], G. Hübner[30], M. Pichler[31], T. Müller[3]

Affiliations

Affiliation addresses are listed at the end of the article.

Key words

- abdomen
- biopsy
- interventional procedures
- percutaneous
- ultrasound

Abstract

Purpose: To analyse the incidence of bleeding after percutaneous ultrasound guided diagnostic and therapeutic intraabdominal interventions in a prospective multicentre study (DEGUM percutaneous interventional ultrasound study).

Materials and Methods: Within a time period of 2 years diagnostic and therapeutic intraabdominal interventions (with the exclusion of ascites paracentesis) performed percutaneously under continuous ultrasound (US) guidance were prospectively assessed using a pseudonymized standardized web site entry form. Number and type of intervention, operator experience, patient characteristics, medication, lab data as well as technical aspects of the procedure and bleeding complications were analysed according to the interventional radiology standards.

Results: 8172 US-guided intraabdominal interventions (liver n = 5903; pancreas n = 501, kidney n = 434, lymph node = 272, biliary system n = 153, spleen n = 63, other abdominal organs and extraorganic targets n = 999) were analysed in 30 hospitals. The majority were diagnostic biopsies including 1780 liver parenchyma, 3400 focal liver lesions and 404 pancreatic lesions. 7525 interventions (92.1 %) were performed in hospitalized patients (mean age 62.6 years). Most operators were highly experienced in US-guided interventions (> 500 interventions prior to the study n = 5729; 70.1 %). Sedation was administered in 1131 patients (13.8 %). Needle diameter was ≥ 1 mm in 7162 punctures (87.9 %) with main focus on core needle biopsies (18 G, n = 4185). Clinically relevant bleeding complications with need of transfusion (0.4 %), surgical bleeding control (0.1 %) and radiological coiling (0.05 %) were very rare. Bleeding complications with fatal outcome occurred in four patients (0.05 %). The frequency of major bleeding complications was significantly higher in patients with an INR > 1.5 ($p < 0.001$)

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Correspondence
Prof. Deike Strobel
Internal medicine I, University of Erlangen
Ulmenweg 18
91058 Erlangen
Germany
Tel.: ++ 49/0 91 31/8 53 50 00
Fax: ++ 49/0 91 31/8 53 52 52
deike.strobel@uk-erlangen.de

Zusammenfassung

Ziel: Blutungskomplikationen sonografisch gesteuerter diagnostischer und therapeutischer intraabdomineller Punktionen sollten prospektiv multizentrisch untersucht werden.

Material und Methoden: Innerhalb von 2 Jahren wurden alle Punktionen (mit Ausnahme von Aszitespunktionen), die unter kontinuierlicher Ultraschallsicht perkutan erfolgten, mittels pseudonymisierter webbasierter Eingabemasken erfasst: Anzahl und Art der Interventionen, Untersucherfahrung, Patientencharakteristika, Medikation, Laborbefunde und Blutungskomplikationen.

Ergebnisse: 8172 Punktionen wurden in 30 Krankenhäusern erfasst (Leber n = 5903; Pankreas n = 501, Nieren n = 434, Lymphknoten = 272, Biliäres System n = 153, Milz n = 63, andere abdominelle Organe and extraorganische Ziele n = 999). Die Mehrzahl der Punktionen waren diagnostische Biopsien (Leberparenchym n = 1780, fokale Leberläsionen n = 3400, Pankreasraumforderungen n = 404). 7525 Interventionen (92,1 %) erfolgten bei stationären Patienten (mittleres Alter 62,56 Jahre) durch erfahrene Untersucher (> 500 Punktionen vor Studienbeginn n = 5729; 70,1 %). 1131 Patienten (13,8 %) erhielten eine Sedierung. 7162 Interventionen (87,9 %) erfolgten mit Nadeln ≥ 1 mm Durchmesser mit dem Schwerpunkt auf 18-Gauge-Nadeln (n = 4185), 989 Punktionen (12,1 %) erfolgten mit Feinnadeln (< 1 mm). Schwere Blutungen waren selten: transfusionsbedürftige Blutungen (0,4 %), operative (0,1 %) und radiologische (0,06 %) Blutstillung, Blutungen mit Todesfolge (0,05 %). Schwere Blutungskomplikationen traten signifikant häufiger bei einer INR > 1,5 auf ($p < 0,001$) und bei einer Begleitmedikation mit Beeinträchtigung der Thrombozytenaggregration oder der plasmatischen Gerinnung ($p < 0,0333$).

Schlussfolgerungen: Das Spektrum ultraschallgesteuerter intraabdomineller Punktionen ist breit. Diagnostische Leberbiopsien sind die häu-

and patients taking a medication potentially interfering with platelet function or plasmatic coagulation ($p < 0.0333$).

Conclusion: This prospective multicentre study confirms the broad spectrum of percutaneous US-guided intraabdominal interventions. However diagnostic liver biopsies dominate with the use of core needle biopsies (18 G). Percutaneous US-guided interventions performed by experienced sonographers are associated with a low bleeding risk. Major bleeding complications are very rare. A pre-interventional INR < 1.5 and individual medication risk assessment are recommended.

figsten durchgeführten intraabdominellen Punktionen und werden überwiegend mit 18-G-Nadeln durchgeführt. Schwerwiegende Blutungskomplikationen sind bei erfahrenen Untersuchern sehr selten. Die INR sollte präinterventionell < 1,5 sein. Eine Risikobeurteilung des individuellen Blutungsrisikos und der Begleitmedikation des Patienten sollte vor intraabdominellen Punktionen erfolgen.

Introduction

The use of ultrasound for renal biopsies was reported for the first time by Berlyne in 1961 [1]. The first fine-needle aspiration biopsy under direct guidance by ultrasonic scanning (A-mode) was described in 1972 by Goldberg [2] and Rasmussen [3]. In 1975, Hancke and Smith reported on fine-needle biopsy of suspicious solid pancreatic lesions using a compound scanner with a biopsy transducer [4, 5]. Interventional ultrasound was widely practiced after about 1980. Up to now, percutaneous US-guided abdominal interventions are frequently performed as minimally invasive procedures in clinical practice. A flexible choice of puncture route and continuous visualization of the needle position throughout the puncture in real time in addition to the lack of radiation as in computed tomography (CT)-guided interventions [6, 7] make ultrasound (US) the primary imaging device to guide diagnostic or therapeutic interventions. Frequently diagnostic biopsies are performed using fine needles with an outer diameter of less than 1 mm. Fine-needle biopsies are associated with a very low number of complications as known from several studies including two large retrospective surveys of the German Society of Ultrasound in Medicine [9, 10]. However fine-needle aspiration (FNA) is of limited use in obtaining enough material of sufficient quality for a proper histologic diagnosis in parenchymal disorders or tumor differentiation when additional immunostaining or molecular analyses have to be performed [11, 12]. Therefore, core needle biopsies (CNB) are nowadays more frequently used [13]. In addition, larger needle sizes are used for the increasing number of US-guided therapeutic interventions like the drainage of abscesses or symptomatic cysts or tumor ablation. Currently most data on bleeding complications of US-guided interventions are derived from retrospective single center studies [14 – 18] or from multicenter audits or questionnaires [9, 10, 19 – 21]. Prospective data are limited. Most of the few prospective trials included only a small number of patients and focused on liver parenchyma biopsies [22 – 25]. To address the current spectrum of diagnostic and therapeutic US-guided abdominal interventions, we designed a prospective multicenter observational study within the German Society for Ultrasound in Medicine (Deutsche Gesellschaft für Ultraschall in der Medizin, DEGUM). The aim of this prospective multicenter study presented in this manuscript was to evaluate the incidence of bleeding complications after percutaneous ultrasound-guided intraabdominal diagnostic and therapeutic interventions.

Methods

Study design

A 2-year prospective multicenter study was designed. Only percutaneous US-guided interventions with continuous visualization of the puncture procedure were included. Blind or US-assisted biopsies (after initial targeting by US) as well as ascites punctures or ascites drainages were excluded. The study design using pseudonymized patient data was approved by the ethical review board of the University of Erlangen (No. 4129). The invitation to participate in the national DEGUM intervention study was announced on the DEGUM homepage and via personal communication at national and regional DEGUM conventions. Study participation was restricted to US units with a frequency of at least 50 interventions per year performed and lead by an experienced physician (DEGUM II and III level). All recruited centers were committed to prospectively document all consecutive US-guided intraabdominal diagnostic and therapeutic interventions on a standardized pseudonymized online data form within the study period. All patients had to give informed consent to the documentation of their pseudonymized data according to a standardized protocol.

Study population

The pseudonymized data form included basic data about the center like the level of interventional experience of the performing physician (< 100, > 100 – < 500 and > 500 US-guided abdominal punctures prior to the start of the study), baseline data of the patient undergoing puncture (gender, age, INR, platelet count, clinically known liver cirrhosis or known diseases with an increased risk of bleeding as coagulation factor deficiency, inpatient or outpatient). Type, target and procedural aspects of interventions, technical parameters, periinterventional medication and postinterventional bleeding were analyzed. Detailed information of all parameters included in the standardized study protocol is given in **Table 1**.

Classification of bleeding complications

The classification of minor and major complications was done according to the Society of Interventional Radiology (SIR) Standards of Practice Committee Classification of Complications by Outcome [33]. Minor complications are defined as an event with either no consequence (grade A) or only nominal therapy (B). Major complications are defined as events that require therapy (C), lead to an unplanned increase in the level of care (D), permanent sequelae (E) or even death (F). According to the SIR guidelines major bleeding in the study design was defined by the need for erythrocyte concentrates (RBC transfusion), circulatory relevant bleeding with shock or intensive care monitoring, radiological or surgical bleeding control or death.

Table 1 Pseudonymized online data sheet.

premedication	– platelet aggregation inhibitors within 7 days prior to intervention – new oral anticoagulants (such as dabigatran, rivaroxaban, and apixaban) within 48 hours prior to intervention – low molecular weight heparine (LMWH) on day of intervention – non-steroidal anti-inflammatory drugs (NSAID) on day of intervention – platelet concentrates or fresh frozen plasma within 12 hours prior to intervention
medication	– use of additional analgosedation at the time of puncture
intervention type	– diagnostic – therapeutic
target	– liver – parenchyma or focal lesion – pancreas – kidneys – parenchyma or focal lesion – spleen – lymph nodes – gastrointestinal tract – other
technique	– type of US probe (curved array, linear array) – needle guidance (free-hand, puncture device, dedicated puncture US probe) – needle diameter – needle type (tru-cut, vacuum, other) – needle propagation within the target (automated high speed system, manually)
procedure	– potential passage of interfering organs – number of needle passes – use of contrast-enhanced US for target visualization
post-interventional	– pain due to intervention with need for analgesic medication within 24 h after the procedure – development of free fluid in abdominal US within 24 h after the procedure – decline in hemoglobin levels ≥ 2 g/dl within 24 h after the procedure – RBC transfusion within 48 h after the procedure – circulatory relevant bleeding with shock or intensive care monitoring – radiological bleeding control (coiling) – surgical bleeding control – prolongation of hospital stay or re-hospitalization – intervention-related death

Statistics

Statistical analysis was performed using the SAS statistical software version 9.1.3 (SAS Institue, Inc., Cary, NV, USA). Exploratory analyses were undertaken for all variables. Data was analyzed descriptively with respect to the complication rate, absolute and relative frequency, mean, standard deviation, median, and maximum and minimum values. Major and minor bleeding complications were analyzed descriptively. Statistical analysis was focused on major bleeding complications with clinical symptoms. Potential risk factors (liver cirrhosis, INR, platelet counts, medication associated with an increased bleeding risk, needle diameter, needle passes) were assessed for correlation with complication rate using the $\chi 2$-test. Subsequently, bivariate logistic regression was performed. Due to the small number of complications, a multivariate analysis could not be performed. All statistical tests were two tailed. The significance level was set at $\alpha = 5\%$ ($p < 0.05$). Major complications were looked at individually. Patient reports were checked individually in case of surgical intervention, radiological intervention or fatal outcome.

Table 2 Patient characteristics.

	N	%
patient number (total)	8172	100
age (years, mean, range)	62.56 (11 – 97)	
gender (m/f)	4596/3576	56.2/43.8
liver cirrhosis present/absent	916/7256	11.2/88.8
INR normal	7125	88.3
INR 1.3 – 1.5	831	10.2
INR > 1.5	125	1.5
platelet count > 100 000/µl	7671	93.9
platelet count 50 000 – 100 000/µl	436	5.3
platelet count < 50 000 /µl	65	0.8
platelet aggregation inhibitors < 7 days prior to puncture[1]	567	6.9
LMWH at day of puncture[1]	703	8.6
NSAID at day of puncture[1]	164	8.6
new oral anticoagulants within 48 hours prior to puncture[1]	26	0.2

[1] single and combined medication included.

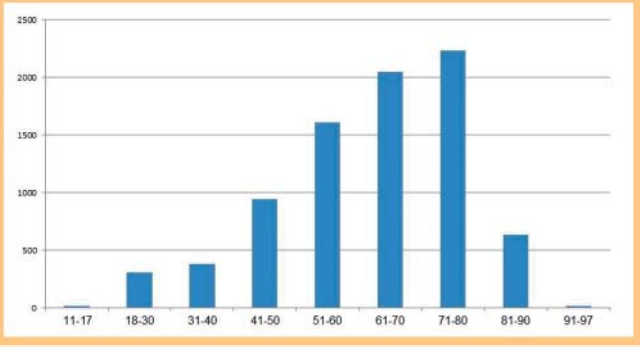

Fig. 1 Patient age. The age of patients subdivided into years 11 – 17 (n = 15; 0.2 %), 18 – 30 (n = 301; 3.7 %), 31 – 40 (n = 381; 4.7 %), 41 – 50 (n = 940; 11.5 %), 51 – 60 (n = 1609; 19.7 %), 61 – 70 (n = 2047; 25.0 %), 71 – 80 (n = 2233; 27.3 %), 81 – 90 (n = 633; 7.7 %) and 91 – 97 (n = 13; 0.2 %).

Results

Participating centers

8172 percutaneous US-guided intraabdominal interventions were performed in 30 participating centers from January 2011 to December 2012. The number of interventions per center ranged from < 150 (n = 10), 151 – 250 (n = 10), 251 – 500 (n = 6) to high volume centers with > 500 – 919 interventions (n = 4). Most participating physicians (DEGUM level 2 and DEGUM level 3) were highly experienced in US-guided interventions: 5729 interventions (70.1 %) were performed by physicians with more than 500 interventions done prior to the study, 1444 interventions (17.7 %) were performed by physicians with 100 – 500 interventions prior to the study and 999 interventions (12.2 %) were performed by physicians with < 100 interventions prior to the study.

Patient characteristics

Patient characteristics are described in **Fig. 1**, **Table 2**. Known coagulation factor deficiencies were very rare (n = 2/8172; 0.04 %), including hemophilia B and inherited factor XIII deficiency. The majority of patients had normal values for INR and platelet counts. 1100/8172 patients (13.46 %) had taken a medication

interfering with platelet function or plasmatic coagulation (platelet aggregation inhibitors within 7 days prior to puncture; new oral anticoagulants within 48 hours prior to puncture; LMWH or NSAID on the day of puncture). On the day of puncture platelet concentrates were administered in 0.6 % of interventions and fresh frozen plasma was given in 1.0 % of interventions. The administration in patients suspected of having a higher risk of bleeding was based on the clinical judgment of the operator.

Procedural medication

Local anesthesia of the puncture site was performed in all US-guided intraabdominal punctures. However pre-interventional intravenous short-time sedation was used only by some operators in individual patients. The majority of interventions were done with local anesthesia of the puncture site only. Sedation was administered in 1131/8172 patients (13.8 %) prior to puncture. Analgesic medication was given during the intervention or up to 24 hours after the intervention in 737/8172 patients (9.0 %).

Technical and procedural parameters

Technical and procedural aspects are described in **Table 3**. Whereas the majority of US-guided abdominal interventions was performed in free-hand technique (57 %), puncture devices or dedicated ultrasound probes were used in 20.1 % and 22.8 %, respectively. The distance from the skin surface was measured when puncturing focal lesions (n = 7251). The mean distance to the anterior border of the focal lesions was 5.04 ± 2.68 cm with a maximum distance of 20 cm. A broad spectrum of needle types was used. However, the most frequently used needle types were Tru-cut biopsy needles (36.1 %), followed by tri-axial core biopsy needles (16.5 %) and vacuum-assisted core biopsy needles (8.2 %). The outer needle diameter varied from an outer diameter of 0.8 mm to > 5 mm in drains. The most frequently used needle diameter was 1.3 mm (18 G) in 4185 interventions (51.2 %) (**Fig. 2**). In abscess drainage, single lumen pigtail catheters were mainly used (n = 601 drains). Double lumen catheters were rarely used (n = 28 drains). The most frequently used drain diameter was 3.3 mm (10 French) in 437 interventions. In liver tumor ablation radiofrequency (RFA) was the dominant ablation technique. 92.1 % of all procedures were performed in hospitalized patients.

Target and type of intervention

The most common target of US-guided intraabdominal punctures was the liver, followed by the pancreas and the kidneys. Intraabdominal targets with a rate lower than 5 % of the total study population covered a broad variety of targets, like lymph nodes, the biliary system, the gastrointestinal tract, the spleen, the adrenal glands and other intraabdominal puncture sites including extra-organic masses and collections (**Fig. 3**). Most liver punctures were performed for diagnostic purposes: 87.8 % were diagnostic liver biopsies (n = 1780 parenchyma 30.2 %; n = 3400 focal lesions, 57.6 %) versus 12.2 % therapeutic liver interventions. In pancreatic punctures, 80.6 % were diagnostic biopsies and 19.4 % were therapeutic interventions.

Frequency and spectrum of complications

The overall rate of major bleeding complications was 0.43 %. Major bleeding complications with changes of vital signs, shock or intensive care management and the need for erythrocyte transfusion occurred in 19 patients (0.23 %). Major bleeding complica-

Table 3 Technical and procedural parameters.

	N	%
ultrasound probe (curved array/linear array)	7365/807	90.1/9.9
needle guidance (free-hand/puncture device/dedicated puncture ultrasound probe)	4660/1645/ 1867	57.0/20.1/ 22.8
needle propagation within the tissue (automated system/manually)	4854/3318	59.4/40.6
needle diameter (≥ 1 mm/< 1 mm)	7162/989	87.9/12.1
inpatient procedure/outpatient procedure	7525/647	92.1/ 7.9
use/no use of echo-enhancing agent	1034/7138	12.7/87.3
number of needle passes (1/2/> 2)	5191/2033/948	63.5/24.9 /11.6
passage/no passage of interfering organs	398/7774	4.9/95.1

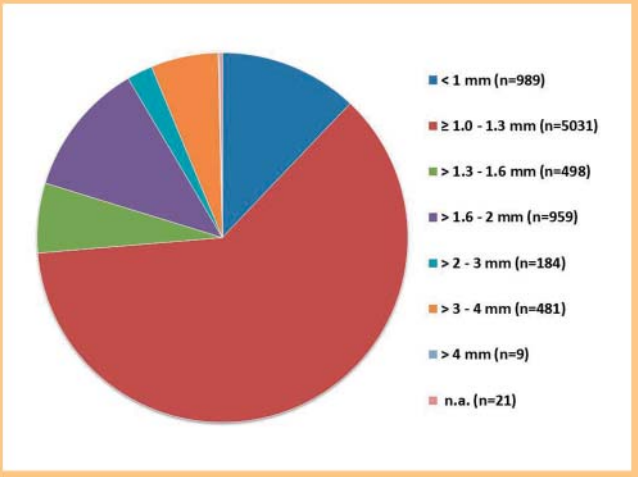

Fig. 2 Needle diameter. The outer needle diameter ranged from 0.8 mm to > 5 mm. The most frequently used needle diameter was 18G.

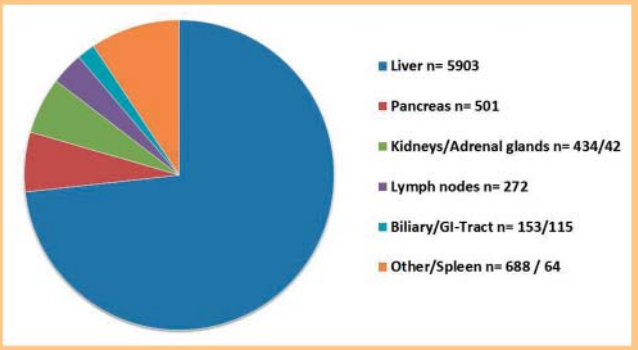

Fig. 3 Target of intervention. The most common target of US-guided intraabdominal puncture was the liver (n = 5903; 72.2 %), followed by the pancreas (n = 501; 6.1 %) and the kidneys (n = 443; 5.4 %). Intraabdominal targets with a rate lower than 5 % of the total study population covered a broad variety of targets, like lymph nodes (n = 272; 3.3 %), the biliary system (n = 153; 1.9 %), the gastrointestinal tract (n = 115; 1.4 %), the spleen (n = 63; 0.08 %), the adrenal glands (n = 42; 0.05 %) and other intraabdominal puncture sites including extra-organic masses and collections.

Table 4 Major bleeding complications given in absolute numbers and % related to target or intervention.

	intervention number	major complications	clinically severe hemorrhage	laparotomy	radiological coiling	death
total	*8172*	*35 (0.43 %)*	*19 (0.23 %)*	*8 (0.10 %)*	*4 (0.05 %)*	*4 (0.05 %)*
liver	**5903**	**23 (0.39 %)**	**13 (0.22 %)**	**6 (0.10 %)**	**1 (0.02 %)**	**3 (0.05 %)**
parenchyma	1780	3 (0.17 %)	2 (0.11 %)	1 (0.06 %)	0	0
focal lesion	3400	19 (0.56 %)	11 (0.32 %)	4 (0.12 %)	1(0.03 %)	3 (0.09 %)
therapeutic	723	1(0.14 %)	0	1 (0.14 %)	0	0
pancreas	**501**	**3 (0.60 %)**	**2 (0.40 %)**	**1 (0.20 %)**	**0**	**0**
diagnostic	404	2 (0.49 %)	2 (0.49 %)	0	0	0
therapeutic	97	1 (1.03 %)	0	1(1.03 %)	0	0
kidney	**434**	**4 (0.92 %)**	**1 (0.23 %)**	**0**	**3 (0.69 %)**	**0**
parenchyma	363	4 (1.10 %)	1 (0.27 %)	0	3 (0.83 %)	0
focal lesion	71	0	0	0	0	0
spleen	**63**	**2 (3.17 %)**	**1 (1.59 %)**	**1 (1.59 %)**	**0**	
lymphnode	**272**	**1 (0.37 %)**	**0**	**0**	**0**	**1 (0.37 %)**
other	999	2 (0.31 %)	2 (0.31 %)	0	0	0

tions with subsequent surgical bleeding control were observed in 8 patients (0.10 %). Major bleeding complications with subsequent radiological coiling were observed in 4 patients (0.05 %). Death related to intervention was observed in 4 patients undergoing diagnostic biopsies (0.05 %). No death related to therapeutic intervention was observed. Only 1/35 major bleeding complication occurred in a patient with liver cirrhosis. Detailed information on major complications in relation to the type and target of the intervention is given in **Table 4**.

Bleeding with fatal outcome

Fatal outcome occurred in four patients (0.05 %). Impaired INR values of 1.3 – 1.5 or INR values > 1.5 were present in 3/4 patients, including two patients with pre-interventional low platelet counts 50 000 – 100 000/µl. Medication potentially interfering with platelet function or plasmatic coagulation was taken by two patients, including platelet aggregation inhibitors in one patient and a combined medication of NSAID and platelet aggregation inhibitors in another. The needle type and diameter were Tru-cut 1.3 mm (n = 2), vacuum 1.2 mm (n = 1), vacuum 1.7 mm (n = 1). One needle passage was performed in 3/4 patients, more than 2 needle passages in one patient. A fatal outcome occurred in three diagnostic biopsies of liver metastases and one diagnostic biopsy of a lymph node metastasis despite surgical (n = 2) or radiological (n = 1) intervention. In detail, the four fatal outcomes were due to intraabdominal bleeding after biopsies of

1. A liver metastasis in an 80-year-old woman (final diagnosis metastatic urothelium carcinoma), surgical bleeding control failed
2. A liver metastasis in a 72-year-old male patient (final diagnosis of a metastatic low-grade adenocarcinoma of the esophagus), surgical bleeding control failed
3. A liver metastasis in an 89-year-old male patient (final diagnosis: metastatic rectum carcinoma), radiological embolization failed
4. An abdominal lymph node in an 86-year-old patient (final diagnosis: metastatic disease), intensive care unit therapy was limited due to unfavorable prognosis.

Major nonfatal bleeding complications

The rate of major nonfatal bleeding complications was 0.38 %. 8/8172 patients (0.1 %) had to undergo laparotomy to stop severe intraabdominal bleeding including six with diagnostic biopsies (liver: two metastases, one hepatocellular carcinoma, one hepatic angiosarcoma, one hepatic extramedullary hematopoiesis; one spleen metastasis) and two patients with therapeutic drains (pancreatic abscess and symptomatic liver cyst). Impaired INR values of 1.3 – 1.5 or INR values > 1.5 were present in 4/8 patients, including two patients with pre-interventional low platelet counts of 50 000 – 100 000/µl. Mediation potentially interfering with platelet function or plasmatic coagulation was taken by only 2/8 patients (NSAID and platelet aggregation inhibitors).

In addition 4/8172 patients (0.05 %) with diagnostic biopsies (renal parenchyma n = 3, liver metastasis n = 1) had to undergo radiological coiling to stop post-interventional bleeding. None of the patients undergoing radiological coiling had an impaired INR value or had taken a medication potentially interfering with platelet function or plasmatic coagulation.

Clinically severe hemorrhage causing cardiovascular reactions associated with intensive care monitoring and erythrocyte transfusion (but no surgical or radiological intervention) occurred in 19/8172 patients (0.23 %) including 18 diagnostic biopsies (liver metastasis n = 8, benign liver lesions n = 3, benign pancreatic lesions n = 2, liver parenchyma n = 2, spleen parenchyma n = 1, renal parenchyma n = 1, extra-organic lesion n = 1) and one therapeutic intervention (extra-organic abscess drainage).

Influence of center volume and physician experience

The number of interventions per center ranged from ≤ 150 (n = 10), 151 – 250 (n = 10), 251 – 500 (n = 6) to high-volume centers 501 – 919 (n = 4). The frequency of major complications ranged from 0.36 % to 0.56 % in high-volume centers. The major complication rates in other participating centers ranged from 0 – 1.21 % (251 – 500 interventions), 0 – 1.3 % (151 – 250 interventions) to 0 – 1.48 % (≤ 150 interventions). 5729 of the total of 8172 interventions (70.1 %) were performed by physicians with more than 500 interventions done prior to the study. The percentage of major complications in relation to the experience of the physician (number of interventions performed prior to the study) was 11.4 % (< 100), compared to 34.3 % (100 – 500) and 54.3 % (> 500).

Table 5 Medication and bleeding complications.

total	medication interfering with platelet function or plasmatic coagulation	no medication interfering with platelet function or plasmatic coagulation	P-value
major bleeding complications	9/1100 (0.82 %)	26/7072 (0.37 %)	*0.0333*
no major bleeding complications	1091/1100 (99.18 %)	7046/7072 (99.66 %)	
single medication	platelet aggregation inhibitors	no platelet aggregation inhibitors	
major bleeding	4/432 (0.93 %)	31/7740 (0.40 %)	0.1036
no major bleeding	428/432 (99.07 %)	7709/7740 (99.60 %)	
single medication	LMWH	no LMWH	
major bleeding	3/560 (0.54 %)	32/7612 (0.42 %)	0.6867
no major bleeding	557/560 (99.46 %)	7580/7612 (99.58 %)	
single medication	NSAID	no NSAID	
major bleeding	2/92 (2.17 %)	33/8080 (0.41 %)	*0.0099*
no major bleeding	90/92 (97.83 %)	8047/8080 (99.60 %)	
combined medication	platelet aggregation inhibitors and NSAID	no platelet aggregation inhibitors and NSAID	
major bleeding	2/23 (8.69 %)	33/8149 (0.40 %)	*< 0.0001*
no major bleeding	21/23 (91.31 %)	8116/8149 (99.60 %)	

Influence of INR and platelet counts

In patients with major bleeding complications, the rate of impaired INR values was higher compared to patients with no major bleeding complications (INR 1.3 – 1.5 20.0 % vs. 10.1 % and INR > 1.5 11.4 % vs. 1.5 %). The rate of major bleeding complications was 9.8 times higher for patients with an INR > 1.5 compared to a normal INR at bivariate logistic regression (OR 9.824, 95 %CI 3.358 – 28.741, p = 0.0010). The rate of major bleeding complications was 2.5 times higher for patients with an INR from 1.3 to 1.5 compared to a normal INR at bivariate logistic regression (OR 2.545, 95 % CI 1.093 – 5.026, not significant). Impaired INR values were present in six patients (n = 4 INR1.3 – 1.5, n = 2 INR values > 1.5) and a low platelet count in three patients (50 000 – 100 000/µl: n = 2 and < 50 000/µl: n = 1). Additional four patients had impaired INR values combined with low platelet counts. The rate of major bleeding complications was not significantly higher in patients with low platelet counts compared to normal platelet counts at bivariate logistic regression (p = 0.3611).

Influence of medication associated with a potential bleeding risk

The rate of major bleeding complications was statistically higher in patients taking a medication potentially interfering with platelet function or plasmatic coagulation (n = 9/1100; 0.82 %) compared patients with no medication (n = 26/7072; 0.37 %) (p = 0.0333) (**Table 5**).

1100/8172 patients (13.46 %) had taken a medication interfering with platelet function or plasmatic coagulation (platelet aggregation inhibitors within 7 days prior to puncture; new oral anticoagulants within 48 hours prior to puncture; LMWH or NSAID on the day of puncture). With respect to a single specific medication, the rate of major bleeding complications was statistically higher in patients taking an NSAID (n = 2/92; 2.17 %) versus no NSAID (n = 33/8080; 0.41 %) (p = 0.0099). With respect to a combined medication interfering with platelet function or plasmatic coagulation, the rate of major bleeding complications was statistically higher in patients taking platelet aggregation inhibitors and an NSAID (n = 2/23; 8.69 %) versus no combined medication of platelet aggregation inhibitors and an NSAID (n = 33/8149; 0.40 %) (p < 0.001). In other combined medications potentially interfering with platelet function or plasmatic coagulation, no significant change in the rate of major bleeding complications was seen. In the 35 patients with major bleeding complications, platelet aggregation inhibitors were taken by 3/35 patients (8.6 %), NSAIDs were taken by 3/35 patients (8.6 %) and LMWHs had been given to three patients (8.6 %). Combined medication was assessed in 3/35 patients (platelet aggregation inhibitors and NSAID n = 2; platelet aggregation inhibitors and LMWH n = 1). No new oral anticoagulants were taken by any of the 35 patients with major bleeding complications.

Influence of technical parameters

There was no significant increase in major bleeding complications with respect to needle diameter, needle passage (one, two or more than two passages), distance to target and size of focal liver lesions. With respect to the needle, no comparison between CNB and FNA can be made due to the low number of FNA in our study cohort.

Minor complications

Minor complications were defined as events with either no consequence or only nominal therapy. Minor complications included the occurrence of free abdominal fluid within 24 hours after intervention (US mandatory) in 443 patients (5.42 %), a decline in hemoglobin levels more than 2 g/dL in 72 patients (0.88 %) and post-interventional pain with the need of analgesic medication in 737 patients (9.01 %). Overall post-interventional erythrocyte transfusion was given in 36/8172 patients (0.44 %) without clinical signs of shock or need for surgical or radiological interventions: in 19 of these patients free abdominal fluid was seen on post-interventional US, 14 had a post-interventional decline of hemoglobin levels of more than 2 g/dL, 8 had both (free fluid with a hemoglobin decline) and 10 patients had neither.

Discussion

Percutaneous biopsy performed under US assistance or US guidance is a routine diagnostic procedure in most hospitals [12]. US is the first choice imaging technique for interventions due to advantages like continuous real-time visualization of the needle tip and flexible puncture planes in addition to the lack of radiation exposure and low costs [7, 8]. In US-guided diagnostic biopsies, fine needles had been replaced to a large extent by needles

Table 6 Selected citations related to bleeding complications and mortality.

study	year of publication	study design	needle type	organ punctured	no.of biopsies	% major hemorrhage[1]	% mortality
Livraghi [27]	1983	retrospective	FNA	abdomen	11 700	0.6	0.008
Smith [28]	1984	questionnaire	FNA	abdomen	63 108	not specified	0.006
Gebel [29]	1986	retrospective, monocentric	FNA	abdomen	2072	0.39	0.096
Weiss [9]	1988	questionnaire	FNA	mix[2]	60 949	0.02	0.008
Fornari [30]	1989	retrospective, multicentric	FNA	abdomen	10 766	0.05	0.018
Nolsoe [31]	1990	retrospective	Variable	mix[2]	8000	0.09	0.037
Smith [35]	1991	questionnaire	FNA	abdomen	16 381	Not specified	0.031
Weiss [10]	1996	questionnaire	FNA	mix[2]	95 070	0.02	0.001
Frieser [16]	2009	retrospective, monocentric	Core < 20 G[3]	liver, pancreas	1923	0.40	0
Atwell [17]	2010	retrospective, monocentric	Core ≤ 20G[3]	abdomen	15 181	0.46	0.019
Strobel	2015	prospective, multicentric	Variable	abdomen	8172	0.43	0.049

[1] Based on details provided about complications.
[2] Mix of abdomen and small parts.
[3] Predominantly used needle type.

of a somewhat larger diameter (mostly 18 G = 1.3 mm) in order to harvest material sufficient for histologic examination and for immunohistochemistry. Whereas two large retrospective surveys of the German Society of Ultrasound in Medicine in 1988 and in 1996 reported almost exclusively on FNA [9, 10], only 12.1 % of US-guided interventions in our prospective multicenter study have been performed using needles with a diameter < 1 mm.

Overall complication rate

Percutaneous intraabdominal procedures guided by US are occasionally associated with serious complications [26]. The results of our prospective study have shown that the overall risk of major bleeding and death due to percutaneous US-guided intraabdominal procedures is very low, 0.43 % and 0.05 %, respectively. The rates of mortality and major bleeding were lower in former DEGUM questionnaires including only FNA, whereas our results compare favorably with the newer data reported in the literature (**Table 6**). However, most data on the frequency of major bleeding complications are derived from retrospective studies, questionnaires or national audits including only liver biopsies. In the UK national audit evaluating image-guided or image-assisted liver biopsy including 3486 patients from 87 radiological departments, the rate of major complications was 0.43 % and 4 hemorrhage-related deaths occurred (0.11 %) [19]. In a nationwide prospective study in France, 2082 liver biopsies were performed in 89 liver units of universities and primary referral hospitals by experienced physicians (> 150 procedures performed in 72 %) and hepato-gastroenterologists in 89 % of the cases [21]. In this study the rate of severe complications was 0.57 % and increased with the number of needle passes and decreased with operator experience, use of atropine, and US guidance. US guidance was used in 56 % of biopsies and sedation was given in 0.46 % of patients. In a small Italian multicenter study on 203 percutaneous liver biopsies (LB) in hepatitis C patients, the rate of major bleeding was 0.4 % [22].

Center volume and physician experience

The overall rate of major bleeding complications in the participating centers ranged from 0 – 1.48 %.The frequency of major complications in four high volume centers was slightly lower than in centers with a lower volume. The majority of interventions were performed by physicians with more than 500 interventions done prior to the study. Interestingly, the percentage of major bleeding complications was lower in biopsies performed by less experienced physicians. The reason for this remains unclear. One speculation could be that interventions with an increased risk for complications are usually not performed by beginners or less experienced physicians. In one retrospective study on liver biopsies the complication rate was 0.7 % for inexperienced examiners compared to 2.0 % for experienced examiners [18]. In two prospective studies and one retrospective study including only liver biopsies, the complication rate was not influenced by the physician's experience [24, 25, 32].

Needle diameter and number of needle passes

For intraabdominal biopsies larger needle diameters (< 20 G) are more frequently used today in the clinical routine. Tissue specimens larger than obtained by FNA are frequently needed for immunohistochemical and molecular tumor classification [11]. In liver parenchyma biopsies, the correct staging and grading of chronic hepatitis is based on a liver specimen with a sufficient number of portal tracts [12]. It is notable that only 12.1 % of all punctures in our prospective study were performed with fine needles (defined as an outer diameter less than 1 mm). The majority of interventions were performed with a needle diameter of 18 G (1.3 mm) or larger. To address a statically significant difference in bleeding complications, a total of 14 386 patients would be needed with a sample volume of 7184 FNA and core needles each. Whether larger needle sizes are associated with a higher rate of clinically relevant complications compared to FNA is still a matter of debate. Numerous studies showed no difference in complication rates between the widely used 18 G needles and 'fine needles' [16, 36 – 38], while others demonstrated an increased bleeding rate using 18G needles [18]. In an experimental

animal study on liver biopsies in laparotomy using only Chiba-type needles, larger needle diameters generally produced more bleeding. However, the differences were statistically significant only when comparing 14 G with 16 G needles and 16 G needles with the group of 18 G, 20 G, and 22 G needles [39]. In a retrospective single center study covering 2229 US-assisted and US-guided liver biopsies over 10 years, the overall complication rate was 1.2 %, of which 0.5 % were classified as major and 0.7 % as minor complications. A significant increase in complications involving bleeding was observed with larger needles compared with smaller needles and for cutting biopsies compared with aspiration biopsies (Menghini technique) [18]. Only one prospective study of a large number of blind percutaneous liver biopsies reported the number of needle passes to be a significant risk factor for major hemorrhages [40]. In a 20-year retrospective study of percutaneous liver biopsy including 1398 patients of a major Australian academic hospital, two or more biopsy passes did not increase the risk of bleeding. However, minor complications (pain, vasovagal reaction, vomiting) increased [20]. In our prospective multicenter study we found no correlation between needle diameter, number of needle passes and distance to target and major bleeding complications.

Biopsy targets

Data from prospective studies on the incidence of bleeding complications using a larger needle diameter are limited and focused on diagnostic liver parenchyma biopsies only [21 – 25]. In our prospective study with a broad spectrum of diagnostic and therapeutic interventions, the rate of post-interventional erythrocyte transfusion was 0.44 %. In a retrospective single center analysis on 1923 diagnostic and therapeutic interventions in the liver and pancreas using 18G needles or larger, the bleeding complication rate with the need for erythrocyte transfusion was 0.4 % [16]. In a large retrospective single center review of 15.181 percutaneous CNBs (20G or larger) obtained under CT or US guidance, a rate of 0.5 % severe hemorrhage according to the classification of common terminology Criteria for Adverse Events (CTCAE grade 3 or greater, including transfusion, radiological or surgical interventions and deaths) was found. Like our study, this large retrospective trial includes a variety of intraabdominal targets. In this study, the incidence of bleeding after liver biopsy was 0.5 %; kidney biopsy, 0.7 %; lung biopsy, 0.2 %; pancreas biopsy, 1.0 %; and other biopsy, 0.2 %. The three reported fatalities occurred after biopsies of liver masses [17]. In our study, the major bleeding complication rate was the highest in spleen biopsies (3.17 %) and lower in kidneys (0.92 %), pancreas (0.61 %), liver (0.39 %) and lymph node (0.37 %). Compared to the study of Atwell, the incidences of severe bleeding after liver and pancreas punctures were slightly lower in our study, whereas the incidence of severe bleeding after kidney biopsies was slightly higher. In our study major complications with fatal outcome were very rare (0.05 %), including three punctures of focal liver lesions and one of a lymph node. Whether the risk of bleeding is increased in malignant lesions compared to parenchyma biopsies is still an unanswered question [18, 40]. In our study, three major bleeding events were found in biopsies of liver parenchyma compared to 19 in biopsies of liver masses probably due to the higher tumor vascularity. Interestingly, the rate of major bleeding complications in therapeutic interventions was not increased compared to diagnostic punctures in the liver. In the study of Frieser et al., the rate of major bleeding complications was increased in therapeutic interventions compared to diagnostic biopsies with 2 % versus 0.12 % for the liver and 3.2 % versus 1.1 % for the pancreas. Subanalysis of liver and pancreas interventions has to be performed in further studies.

Risk factors

Liver cirrhosis

Liver cirrhosis in this prospective multicenter study was not a risk factor for major bleeding complications. In the study of Frieser et al., including 449 cirrhotic and 1474 non-cirrhotic patients, the rate of post-interventional major bleeding complications was 6.1 % in cirrhotic patients with an INR > 1.5 and 0.5 % in cirrhotic patients with an INR ≤ 1.5 [16].

INR and platelet count

One third of patients with major bleeding complications had impaired INR values (≥ 1.3) or/and low platelet counts (< 100 000/µl). The rate of major bleeding complications increased in patients with INR values higher than 1.5. Our data confirm the recommendation of the pre-procedural assessment of clotting parameters [42]. For percutaneous US-guided intraabdominal interventions, the INR should be below 1.5. The platelet count is generally measured as a standard part of complete blood count. In our study no increased risk for clinically relevant bleeding complications was assessed in patients with platelet counts between 50 000 and 100 000/µl compared to normal. The influence of a platelet count below 50 000/ml in our study failed to show statistical significance for major bleeding complications due to the small number of patients with severe thrombocytopenia in our study. In the multicentric HALT-C trial, the bleeding risk after percutaneous liver biopsy proved to be significantly higher in patients with a platelet count below 60 000 [24]. McVay and Toy reported an incidence of clinically significant bleeding of 3.4 % in 291 patients with mild thrombocytopenia as defined by platelet counts between 50 000 and 99 000/µl. In this retrospective study there was no significant difference between patients with mild hemostatic abnormalities and patients with normal parameters [41]. For percutaneous intraabdominal procedures platelet transfusion is recommended for counts < 50 000 /µl [42]. For liver parenchyma biopsies, a transjugular approach could also be an option in patients with severe thrombocytopenia.

Medication interfering with platelet function or plasmatic coagulation

In our study, the rate of major bleeding complications was slightly higher in patients with a medication interfering with platelet function or plasmatic coagulation. However, the overall number of patients with this medication was very small. In the retrospective review of Atwell [17] including 15 181 image-guided percutaneous core biopsies, the rate of bleeding was not statistically significant in 3195 patients taking aspirin within 10 days prior to biopsy compared with to 11 986 patients not taking aspirin (0.6 % versus 0.4 %; p = 0.34). This minor difference of 0.2 % represents a 50 % increase in bleeding. The bleeding risk associated with the intake of ASS must be weighed against the important implications of aspirin withdrawal like the risk of coronary and cerebrovascular events. Based on the platelet lifespan of approximately 10 days, aspirin withdrawal for 5 days will result in 30 – 50 % platelets with normal function at the time of procedure. In the large database of Atwell et al., stratification on a large number of patients was not possible to determine the optimum period of

aspirin withdrawal. In the current SIR consensus guidelines for the periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions [42], pre-interventional withholding of aspirin for five days is only recommended for procedures with significant bleeding risk like renal biopsy, biliary interventions, nephrostomy tube placement and complex radiofrequency ablation. For procedures with a moderate risk of bleeding like transabdominal liver CNB or intraabdominal abscess puncture or drainage, withholding of aspirin is not recommended. This recommendation is supported by the overall low rate of bleeding complications in diagnostic and therapeutic intraabdominal interventions in our study. We did not differentiate the medication of platelet aggregation inhibitors for aspirin and non-aspirin drugs like Clopidogrel. Pre-interventional withdrawal of Clopidogrel for 4 days is currently recommended for percutaneous intraabdominal image-guided interventions due to life-threatening hemorrhage in some patient reports [42]. Withholding of one dose of LMWH before percutaneous intraabdominal image-guided interventions is recommended [42]. In our study, LMWH on the day of the procedure had no impact on major bleeding complications.

Limitations

Our study was intended to focus on early bleeding complications which were assessed within the first 48 hours. Late complications occurring days or weeks after the intervention have not been evaluated. However, the great majority of complications occur immediately or within 4 hours after the intervention, and 80 – 96 % will take place within 24 hours [16].

Post-interventional management

Clinical patient monitoring is mandatory. Our study design also included mandatory post-interventional ultrasound and testing of hemoglobin levels for 24 hours after the intervention. The presence of free intraabdominal fluid or a 2-point drop in hemoglobin in a clinically asymptomatic patient is without therapeutic consequence. Therefore, the need for post-interventional routine lab testing or ultrasound in asymptomatic patients remains an open question. Comparative studies with and without post-interventional lab testing and ultrasound, including follow-up of potential bleeding complications, are needed. In the clinical routine (outside of study protocols), post-interventional patient management is variable due to local factors and patient comorbidities.

Conclusion

In conclusion, the results of our large prospective multicenter study show that the overall risk of significant major bleeding (0.43 %) and death (0.05 %) due to percutaneous US-guided intraabdominal interventions performed by experienced physicians is very low. Thus, US-guided abdominal interventions are safe. Routine post-procedural US and laboratory testing in asymptomatic patients therefore seem to be dispensable. Major bleeding complications vary between intraabdominal targets and are more frequent in biopsies of the spleen, kidney and pancreas compared to the liver. Technical factors like needle diameter and number of needle passes do not have any impact on major bleeding complications. However, patient-related risk factors like an impaired INR > 1.5 significantly increase major bleeding complications. Therefore, pre-interventional INR < 1.5 and platelets > 50 000/µl (however not proven yet) are recommended. In patients taking a medication potentially interfering with platelet function or plasmatic coagulation a risk assessment balancing thromboembolic events versus bleeding should be performed prior to US-guided intraabdominal interventions.

Abbreviations

CI	confidence interval
CEUS	contrast-enhanced ultrasound
CNB	core needle biopsy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEGUM	Deutsche Gesellschaft für Ultraschall in der Medizin, German Society for Ultrasound in Medicine
FNA	fine-needle aspiration
G	gauge
INR	international normalized ratio
LMWH	low molecular weight heparin
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PIUS	percutaneous interventional ultrasound
SIR	Society of Interventional Radiology
US	ultrasound

Affiliations

1 Internal Medicine 1, University Hospital Erlangen, Germany
2 Department of Internal Medicine, District Hospital Ebersberg, Germany
3 Department of Internal Medicine 1, Municipal Hospital Steinenberg, Reutlingen, Germany
4 Department of Gastroenterology, Municipal Hospital (Waldklinikum Gera gGmbH), Gera, Germany
5 Central Interdisciplinary Ultrasound, Municipal Hospital Trier (Barmherzige Brüder), Trier, Germany
6 Department of Gastroenterology, Central Ultrasound Unit, University Hospital Leipzig, Germany
7 Department of Internal Medicine 1, University Hospital Regensburg, Germany
8 Department of Internal Medicine 1, University Hospital Mainz, Germany
9 Department of Internal Medicine 1, Municipal Hospital (Schwarzwald-Baar), Villingen-Schwenningen, Germany
10 Department of Internal Medicine B, Gastroenterology, District Hospital (Ruppiner Kliniken), Neuruppin, Germany
11 Department of Internal Medicine 2, Municipal Hospital (Caritas), Bad Mergentheim, Germany
12 Department of Internal Medicine/Gastroenterology, Municipal Hospital (Sana Kliniken Lübeck GmbH), Lübeck, Germany
13 Surgery, University Hospital Dresden, Germany
14 Department of Internal Medicine 1, University Hospital Frankfurt, Germany
15 Department of Internal Medicine 1, Municipal Hospital (Karl-Olga-Krankenhaus), Stuttgart, Germany
16 Department of Internal Medicine, District Hospital Helfenstein, Geislingen, Germany
17 Department of Internal Medicine, District Hospital (Krankenhaus Märkisch Oderland GmbH), Wriezen, Germany
18 Department of Medicine and Gastroenterology, Municipal Hospital (Katharinen), Stuttgart, Germany
19 Innere Medicine, District Hospital (SRH Kliniken Sigmaringen), Sigmaringen, Germany
20 Department of Interal Medicine and Gastroenterology, District Hospital Rems-Murr, Winnenden, Germany
21 Depatment of Internal Medicine, Hospital St Hedwig, Berlin, Germany
22 Department of Internal Medicine, Israeli Hospital, Hamburg, Germany
23 Gastroenterology, Hospital Vivantes Humboldt, Berlin, Germany
24 Department of Medicine 2 and Gastroenterology, District Hospital Helios Meiningen, Germany
25 Department of Internal Medicine, District Hospital Gummersbach, Germany
26 Department of Internal Medicine, Hospital Albertinen, Hamburg, Germany
27 Gastroenterology, St. Josefs Hospital (Helios), Bochum, Germany
28 Department of Internal Medicine 2, Municipal Hosital Düren, Germany
29 Department of Internal Medicine, Hospital Leonberg, Germany
30 Department of Internal Medicine, District Hospital Köthen, Germany
31 Campus Innenstadt Gastroenterology, University Hospital Munich, Germany

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