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Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study

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Abstract
Introduction The over-the-scope clip (OTSC) overcomes limitations of standard clips and achieves a more efficient and reliable hemostasis in non-variceal upper gastrointestinal bleeding (NVUGIB). The study aims to evaluate mortality, rebleeding, and mortality after rebleeding of patients in whom the OTSC was used as the first-line endoscopic treatment (FLET) of NVUGIB.
Patients and methods In total, 118 patients (FLET cohort) with a median age of 73.5 years (range 29–93 years; mean (±SD) 71.39 ± 12.39 years) were included. The distribution of patients with respect to risk category revealed a median Rockall score of 7 (range 3–10). For hypothesis testing, the FLET cohort was categorized into three risk groups taking into account the Rockall score: low risk [Rockall risk category (RRC ≤3)], moderate risk (RRC 4–7), and high risk (RRC ≥8). Event rates (mortality, rebleeding, and mortality after rebleeding) observed per risk group were compared to predicted event rates (Rockall cohort) using Fisher's Exact Test.
Results Primary successful hemostasis (PSH) was achieved in 92.4% either by FLET alone or in combination with an additional hemostasis technique in 1.7% (SCS = secondary clinical success). In 7.5% of the FLET cohort PSH could not be achieved. Compared to RRC prediction, mortality after rebleeding was significantly reduced from 27.9 to 10.9% in the high-risk group (RRC ≥8) treated with FLET ($p < 0.011$). Furthermore, the occurrence of rebleeding or continued bleeding was significantly lower in the moderate risk group (RRC 4–7) with 4.9% as well as in the high-risk group (RRC ≥8) with 21.4% compared to the Rockall cohort 24.0 and 53.2%, respectively ($p < 0.001$).
Conclusions This study shows that OTSC is superior to standard care and FLET reduces significantly rebleeding and rebleeding-associated mortality in NVUGIB. For this reason, OTSC could be the treatment of choice as the first-line treatment as an alternative to standard hemostasis techniques in high-risk patients.

Keywords OTSC · First-line treatment · GI Bleeding · NVUGIB · High-risk patients

Abbreviations

FLET	First-line endoscopic treatment
GI	Gastrointestinal
NVUGIB	Non-variceal upper gastrointestinal bleeding
OTSC	Over-the-scope clip
RRC	Rockall risk category
TTS	Through-the-scope

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a serious clinical problem with a mortality rate between 5 and 10% [1–3]. In the last decades, advances in pharmaceutical and endoscopic therapy have significantly reduced further bleeding, as well as the necessity for surgery and consequently mortality rates. But the mortality rate still

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remains high due to the high age of the patients involved and the presence of multiple comorbidities [4, 5]. Standard established endoscopic therapy includes injection therapy, clip application, and thermal hemostasis. Results from a combination of two endoscopic techniques have been shown to be superior to single technique alone and is therefore generally recommended [6].

The classical clipping devices, the so-called through-the-scope (TTS) clips, have their limitations in the treatment of complex and fibrotic lesions and lesions with large vessels. Recent data identified first-line endoscopic treatment (FLET) with OTSC in high-risk bleeding patients of the upper and lower GI tract as a predictor of successful reduction of rebleeding rates and significantly reduces primary failure [7]. The current study aims to investigate the efficacy of OTSC for FLET of only NVUGIB in a multicenter trial. Our hypothesis was that the FLET with the OTSC clip reduces mortality, rebleeding, and rebleeding-associated mortality compared to standard treatment, as represented and predicted by the Rockall cohort and score [8]. The Rockall risk scoring system identifies patients at risk of adverse events following acute upper gastrointestinal bleeding. The risk score includes clinical criteria (age, comorbidity, shock) and endoscopic criteria (diagnosis, stigmata of acute bleeding) as independent risk factors for predicting mortality accurately [8].

We investigated in an approach using a pooled multicentric patient population as one arm and the validated prognosis given by the Rockall scoring system as a quasi-control arm.

Materials and methods

Patient population

We retrospectively assessed patients admitted to the endoscopy unit of the University Hospital Strasbourg (France), University Medical Centre Freiburg (Germany), and St. Bernward Hospital Hildesheim (Germany) between 02/2009 and 09/2016 with NVUGIB. All patients with FLET for NVUGIB were included in this evaluation. Variceal bleeding was excluded from the data pool as the usage of the OTSC is contraindicated for this group. Patient data were gathered by a standardized questionnaire including regular demographic characteristics as well as diagnostic, treatment, and clinical parameters as needed to establish the grouping according to the Rockall scoring system [8]. The research study was approved by the institutional review board (IRB) of all institutions.

In order to categorize patients into low-, medium-, and high-risk groups, several clinical scoring systems were developed in the past to predict rebleeding episodes and mortality during and after treatment. Rockall and colleagues introduced the Rockall scoring system based upon several easily assessable prognostic factors, such as age, presence of circulatory shock, comorbidities, and endoscopic findings.

The score was derived by multivariate analysis in a cohort of patients with NVUGIB and subsequently internally and externally validated in independent cohorts [8, 9]. Up to now, the Rockall score has been supported by several validation studies showing satisfactory of prediction of mortality and rebleeding in elderly patients with acute NVUGIB [10, 11].

By categorizing patients into risk categories (0–10; ascending severity of patient condition), the Rockall scoring system makes it possible to predict rates of mortality and rebleeding per risk category. Outcome events were defined as described in Table 1.

In total, 118 patients with a median age of 73.5 years (range 29–93 years; mean (±SD) 71.39 ± 12.39 years) were included in the evaluation and 28.0% were at least 80 years old. The population was characterized by a major proportion (85.6%) of multimorbid patients suffering from one or more co-existing illnesses (renal, hepatic, cardiac, and/or respiratory co-illnesses, malignant tumors, diabetes mellitus). Of the 118 patients, 65.3% were under platelet antiaggregation or anticoagulant therapy, 47.5% had cardial and 33.1% hepatorenal comorbidities. The distribution of the patient scores assumes a skewed, high-risk population (Fig. 1). One-hundred and twenty OTSC clips were applied in 118 patients (1.02 clips per patient; two patients had two lesions each at different locations. Every lesion was treated with a single clip). There were no technical or procedural failure documented concerning OTSC application in this study, probably also due to a long-term experience in the three centers with the system.

Statistical analysis

Statistical calculations were performed using SPSS version 14 (SPSS Inc. Chicago, IL, USA) and MedCalc version 16.4.3 (MedCalc Software, Ostend, Belgium). For descriptive statistics, the risk of overall mortality and mortality due to rebleeding was calculated by dividing the number of events by the total number of patients per risk category. The risk of rebleeding was calculated by dividing the number of events by the number of applied clips per risk category. Rates of observed and predicted events per risk category were illustrated in a histogram chart.

For hypothesis testing, patients were categorized into three risk groups: low risk (Rockall risk category ≤ 3), moderate risk (Rockall risk category 4–7), and high risk (Rockall risk category ≥ 8). Event rates observed per risk group were then compared to predicted event rates

Table 1 Definitions of outcome events

Outcome event	Definition
Mortality[a]	In-hospital mortality
Rebleeding[b]	Inability to achieve hemostasis by any measures (clinical failure) or events of rebleeding
Mortality after rebleeding[c]	Mortality after either clinical failure or events of rebleeding

[a] For the original patient population, the Rockall scoring system applied the definition of "30-day mortality" after acute upper gastrointestinal hemorrhage [9]

[b] We categorized each rebleeding event or case of continued bleeding where hemostasis could neither be achieved by the use of the OTSC System alone nor in combination with any adjunctive measure (= clinical failure) as a rebleeding event (compare to Rockall et al. [8], Enns et al. [33])

[c] The outcome "mortality after rebleeding" is termed "deaths (rebleed)" in the original study by Rockall et al. [8]

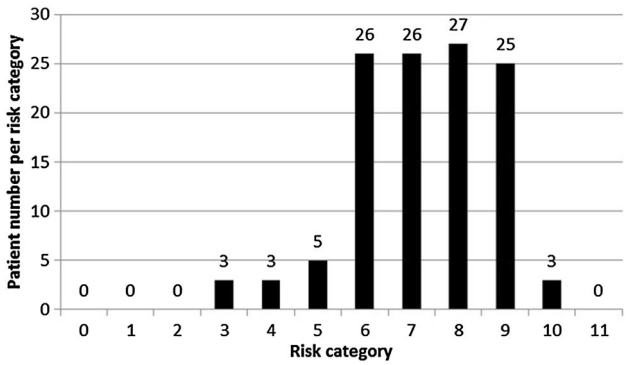

Fig. 1 Number of patients per Rockall risk category ($n = 118$)

(Table 2) using Fisher's Exact Test. p values <0.05 were considered statistically significant.

In order to describe the relationship between the outcomes of interest (mortality, mortality after rebleeding, and rebleeding) and independent predictor variables (presence of hepatorenal comorbidity, presence of cardiac comorbidity, grade of Forrest classification, presence of anticoagulation), a logistic regression was performed using MedCalc. The resulting adjusted odds ratios (ORs) with 95% confidence interval are depicted in Table 3.

Results

In a total of 92.54% of NVUGIB FLET OTSC placement resulted in successful hemostasis either by clip alone (primary clinical success = 90.8%) or in combination with adjunctive measures (secondary clinical success = 1.7%). In 7.5% of clip applications, the bleeding could not be stopped and treatment was defined as clinical failure. The rate of overall in-hospital mortality was 20.3% (24/118 cases).

Fatalities after rebleeding or primary inability to achieve hemostasis occurred in 5.9% of patients (7/118 cases). The total proportion of rebleeding events/primary clinical failures was 13.3% (16/120 clips applied).

Logistic regression analysis revealed a relation between the Forrest classification and the probability of a poor outcome event with regard to mortality, rebleeding, and mortality after rebleeding (Table 3). The presence of antiplatelet or anticoagulation, medication, hepatorenal comorbidity, or cardiac comorbidity did not influence the outcome. Figure 2 depicts the proportion of rebleeding cases per Forrest classification. The high majority of rebleeding cases were in the patient groups with higher Forrest type grades (Forrest type Ia, 11 cases of rebleeding

Table 2 Predicted values for poor outcome events per risk category in NVUGIB patients given by Rockall et al. [8] (indicated in normal type)

	Predicted values for		
Risk category	Mortality (%)	Rebleeding (%)	Mortality after rebleeding (%)
≤3	1.2	7.0/*7.0*	0.4
4	5.3	14.1/*14.4*	2.3
5	10.8	24.1/*18.3*	4.2
6	17.3	32.9/*32.7*	10.9
7	27.0	43.8/*42.3*	18.4
8+	41.1	41.8/*53.2*	27.9

It should be noted in this context that we identified a calculation error in the rebleeding rates published by Rockall et al. in 1999. When recalculating the proportion of rebleeding cases per risk score category, other percentages were found (indicated in italics). Hence, we used the corrected values for the prediction of rebleeding events for further analysis

Table 3 Identification of potential risk factors that determine outcomes of interest

	Overall mortality			Overall rebleeding			Mortality after rebleeding		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Variable									
Forrest classification	0.59	0.36–0.97	0.038	0.29	0.14–0.60	>0.001	0.47	0.27–0.80	>0.01
Anticoagulation	0.77	0.26–2.27	0.642	0.70	0.19–2.61	0.595	0.68	0.23–2.00	0.489
Hepatorenal comorbidity	1.31	0.59–2.89	0.5	1.27	0.50–3.25	0.616	2.00	0.89–4.48	0.091
Cardiac comorbidity	1.65	0.59–4.62	0.338	1.56	0.43–5.73	0.5	1.45	0.50–4.15	0.484

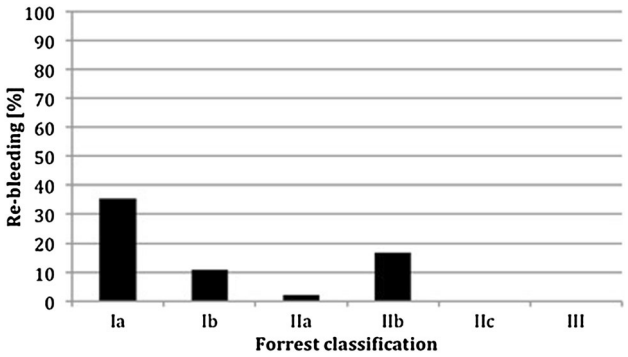

Fig. 2 Rebleeding cases per Forrest classification group in percent. Patients were grouped according to their Forrest classification score

in 31 patients total; Forrest type Ib, 3 cases of rebleeding in 25 patients total). In 60 patients with signs of recent hemorrhage (Forrest type IIa–c), only 2 cases of rebleeding were evident (Forrest IIa 1/52 patients and Forrest type IIb 1/6 patients).

Figure 3 and Table 4 depict the outcome events (mortality, rebleeding, and mortality after rebleeding) per risk category observed in the OTSC patient population compared to the corresponding predicted values given by the validated Rockall scoring system (Table 2). The results show that, by trend, the rate of overall mortality, rebleeding, and mortality after rebleeding decreased with higher risk categories. Except for rebleeding events in patients in risk category 3 and overall mortality of patients in risk score category 7 (statistical outliers), the observed rates for mortality, rebleeding, and mortality after rebleeding were consistently lower than those predicted by the Rockall scoring system, irrespective of the risk category.

Fifty-five patients were assigned to the high-risk group (RRC $\geq$8), 60 patients to the moderate risk group (RRC 4–7), and 3 patients to the low-risk group (RRC $\leq$3). The low-risk group (RRC $\leq$3) included a single case of rebleeding and no fatal events were observed. In the moderate risk group (RRC 4–7), rebleeding occurred in three cases (3 of 61 clips, 4.9%) and a total of eight fatal cases (13.3% overall in-hospital mortality) with one fatal case due to rebleeding or continued bleeding were observed (1.7% mortality after rebleeding). For patients with a high risk (RRC $\geq$8), an overall in-hospital mortality of 29.1% (16 of 55 patients) was observed. In the same risk group, rebleeding occurred in 12 cases (12 of 56 clips, 21.4%) and 6 patients died due to rebleeding or continued bleeding (10.9% bleeding-associated mortality). Compared to Rockall's validated prediction, mortality after rebleeding was significantly reduced from 27.9 to 10.9% in the high-risk group (RRC $\geq$8) treated with the OTSC system as first-line treatment ($p = 0.011$). Furthermore, the occurrence of rebleeding (or continued bleeding) was significantly lower in the moderate risk group (RRC 4–7) with 4.9% as well as in the high-risk group (RRC $\geq$8) with 21.4% compared to 24.0 and 53.2%, respectively, as predicted by the validated Rockall scoring system ($p < 0.001$) (Table 4).

Discussion

Non-variceal upper gastrointestinal bleeding is a severe condition and has an incidence of approximately 35–134 per 100,000 per year [2, 3, 12–16]. In the last decades, endoscopic treatment of NVUGIB has become a gold standard. New endoscopic hemostatic techniques have been developed and improved and their effects on post-interventional outcome analyzed. A meta-analysis including 1156 patients has compared endoscopic clipping versus injection and thermocoagulation in 15 randomized trials [17]. Endoclip treatment was shown to achieve a higher rate of hemostasis than injection alone, but the results of thermocoagulation were comparable with Endoclip. The rebleeding rate after clipping ranged from 7.1 to 9.5%.

TTS clips have their limitations for the treatment of large vessels and fibrotic ulcer ground. Generally, more than one clip is needed to treat the ulcer ground. In the past conventional TTS clips were not able to reopen, so precise positioning of the TTS clips was challenging in particular in angulated positions. New-generation TTS clips have the

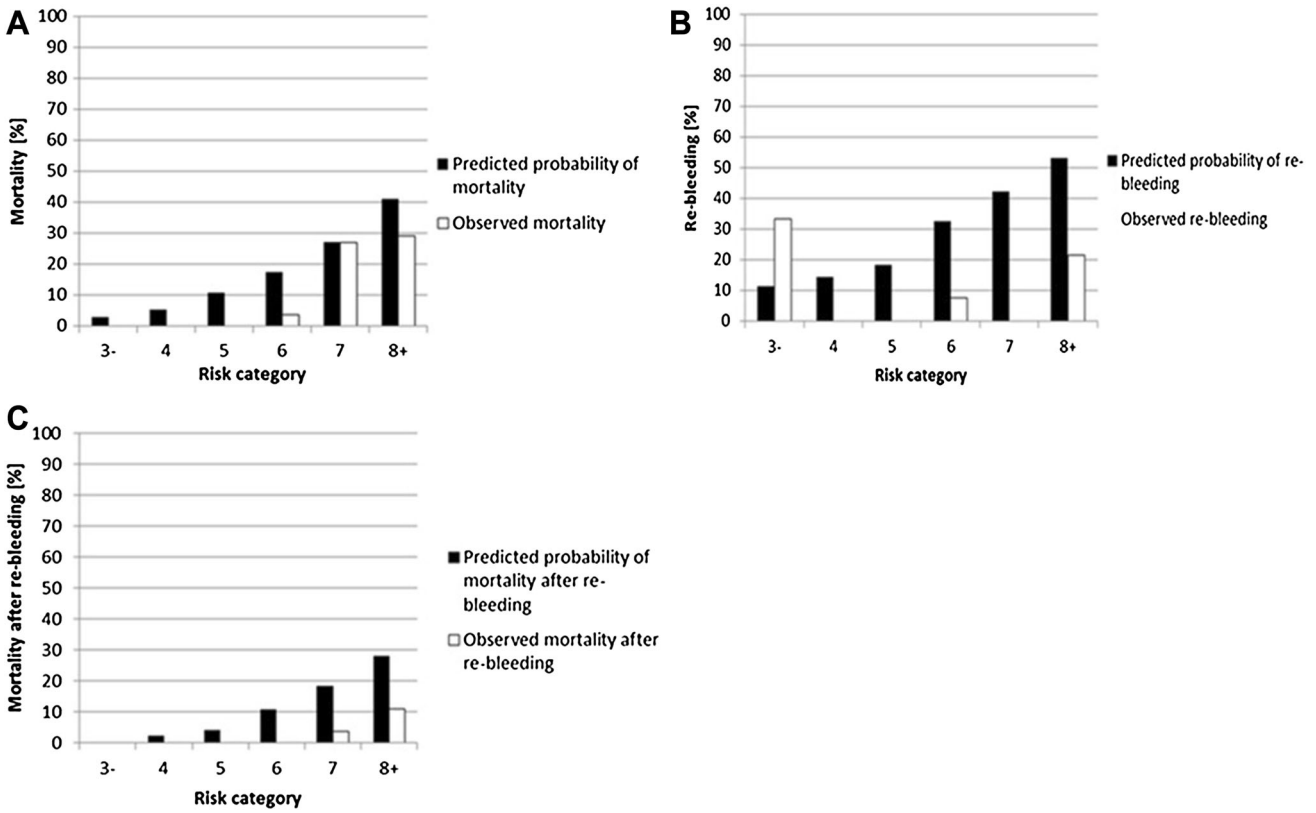

Fig. 3 Predicted versus observed outcomes by risk categories: **A** mortality, **B** rebleeding, and **C** mortality after rebleeding

ability to close and reopen and also the rotability has been improved and aid for a better positioning of the TTS clips at the bleeding site [18].

However, in complex lesions with a fibrotic ulcer base and lesions with large vessels >2 mm, the OTSC has been described to be superior to standard hemoclips [19, 20]. This tool allows mucosal approximation of larger areas and captures deeper tissue layers than TTS clip systems [21]. For the treatment of gastrointestinal perforations and fistulas, the OTSC has already been evaluated and its use has been recommended as a treatment of choice by the respective ESGE position statement on iatrogenic perforations [22–25].

In this multicenter study, the importance of this system as the first-line treatment in NVUGIB was evaluated. In small case series, it has already been proven to be effective as a hemostatic device in NVUGIB [19, 20, 22, 26–28]. Primary hemostasis after NVUGIB was achieved in 85–100% [19, 22, 27]; also, it has been used as the second-line therapy after failure of standard techniques for recurrent bleeding with high success rates [19, 28]. To prove the efficiency of the OTSC regarding mortality, rebleeding, and mortality after rebleeding, the FLET cohort was compared to the Rockall cohort, a cohort representative for the current standard procedure of care [8]. The data of Rockall et al. date back to 1993 and 1994; nevertheless, the endoscopic hemostasis techniques at that time period were comparable to the present therapy [29]. The Rockall score has been routinely used in clinical practice since then, as it predicts accurately patients' overall mortality, rebleeding rate, and mortality after rebleeding within the different risk groups predefined [8].

In this study, we confirmed that higher Forrest status (Forrest Ia) was associated with a higher risk for all three endpoints (mortality, rebleeding, and mortality after rebleeding). The Forrest classification was not included as a risk factor for adverse events in the Rockall prediction, but endoscopic stigmata (blood, adherent clot, and spurting vessel) were included [8]. The Forrest classification has been carefully evaluated and results published showing it as a highly predictive value for rebleeding and mortality [30]. Also in the present study cohort a Forrest Ia bleeding was the main predictive factor for rebleeding also in FLET with the OTSC. One possible reason might be that after detecting the active bleeding site the scope had to be removed for mounting the OTSC on the distal end and reinserted. Due to the continuing Forrest Ia bleeding, the visibility can be significantly impaired leading to an incorrect clip application. This could explain the high rebleeding rate in the Forrest Ia group. But it has been

Table 4 Observed percentages per risk group compared to prediction given by the Rockall scoring system

	Predicted probability of mortality (Rockall) (%)	Observed mortality		*p* value
		% (95% CI)	n/N	
Risk group ≤3	1.2	0 (0–70.8)	0/3	n.a.
Risk group 4–7	13.0	13.3 (5.9–24.6)	8/60	0.847
Risk group 8+	41.1	29.1 (17.6–42.9)	16/55	0.118
	Predicted probability of rebleeding (Rockall) %	Observed rebleeding		
		% (95% CI)	n/N	*p* value
Risk group ≤3	7.0	33 (0–71.0)	1/3	n.a.
Risk group 4–7	24.0	4.9 (1.0–13.7)	3/61	<0.001
Risk group 8+	53.2	21.4 (11.6–34.4)	12/56	<0.001
	Predicted probability of mortality after rebleeding (Rockall) %	Observed mortality after rebleeding		
		% (95% CI)	n/N	*p* value
Risk group ≤3	0.4	0 (0–70.8)	0/3	n.a.
Risk group 4–7	7.3	1.7 (0.1–9.0)	1/60	0.121
Risk group 8+	27.9	10.9 (4.1–22.2)	6/55	0.011

N number of patients per risk group, *n* events per risk group

already shown that Forrest Ia ulcers represent also a different risk category compared to other Forrest categories and have a high risk for rebleeding [30]. On the other hand, once the OTSC is precisely applied with the bleeding vessel accurately inside the clip jaws, the rebleeding risk decreases significantly.

As described, primary overall clinical mortality rate in RCC 4–7 and RCC 8 did not differ from the ones estimated by Rockall [8]. Still, we observed a considerably lower mortality in high-risk group (RCC >8) when compared to the Rockall cohort. This might be explained by a multimorbid FLET cohort with a median Rockall score of 7 and a median age of 73.5 years. Assuming that these prerequisites have a deleterious effect on mortality, logistic regression analysis was performed. Against our expectation, anticoagulant therapy and comorbidities had no influence on mortality in this cohort. Only Forrest classification had significant influence on mortality, rebleeding, and mortality after rebleeding. On the other hand, the risk for rebleeding was significantly reduced in the intermediate (RCC 4–7) and high-risk group (RCC ≥8) compared to the Rockall cohort. The low-risk group did not yield useful data, due to the group size of only three patients.

We could show that FLET with OTSC had a statistically significant effect on reducing rebleeding and rebleeding-associated mortality in comparison to standard procedure of care as described in the Rockall cohort. Overall mortality of all causes was considerably reduced, but not statistically significant.

In a single-center study, Richter-Schrag et al. [31] demonstrated already a trend reducing the rebleeding-associated mortality in the RCC 7 group in comparison to the Rockall cohort 13.9 versus 22.3% ($p = 0.247$) . These results were confirmed in the present multicenter study and mortality after rebleeding was significantly reduced in the high-risk group (RCC 7+).

The limitation of our evaluation is that it is based on retrospective multicentric pooling of prospectively documented endoscopic and clinical data, to create the reference for the Rockall scoring as a quasi-control. However, this approach allowed us to compare our real FLET outcome with the respective prognostic outcome that would have been expected for our patients under standard therapy represented by the Rockall score. Nevertheless, a further limitation of the quasi-control group is that there have also been improvements of clip and hemostatic technology in the last decades, so that the Rockall cohort may not fully reflect this development.

We conclude that OTSC clearly has an advantage when it comes to endoscopic hemostasis for larger and more complex bleeding sites or difficult locations [32]. In particular, in complex and fibrotic lesions it seems to be superior to standard hemoclips and combination therapy. This study confirms that FLET with the OTSC reduces significantly rebleeding rates and mortality after rebleeding in a high-risk cohort and could be an alternative first-line treatment in patients with a high clinical risk, as measured by the Rockall Score.

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Compliance with ethical standards

Disclosures Edris Wedi, Andreas Fischer, Jürgen Hochberger, Carlo Jung, Sinan Orkut and Hans-Jürgen Richter-Schrag have no conflicts of interest or financial ties to disclose.

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