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International multicenter study comparing demographics, therapy and outcomes in bleeding from Mallory Weiss tears and peptic ulcers

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ABSTRACT

Background and study aims Mallory Weiss tears (MWTs) are relatively uncommon causes of upper gastrointestinal bleeding (UGIB), and patients are generally considered at low risk of poor outcome, although data are limited. There is uncertainty about use of endoscopic therapy. We aimed to describe and compare an international cohort of patients presenting with UGIB secondary to MWT and peptic ulcer bleeding (PUB).

Patients and methods From an international dataset of patients undergoing endoscopy for acute UGIB at seven hospitals, we assessed patients with MWT bleeding, including the endoscopic stigmata and endoscopic therapy applied. We compared baseline parameters, rebleeding rate, and 30-day mortality between patients with MWT and PUB.

Results A total of 3648 patients presented with UGIB, 125 of whom (3.4 %) had bleeding from a MWT. Those patients were younger (61 vs 69 years, $P<0.0001$) and more likely to be men (66 % vs 53 %, $P=0.006$) compared to the patients PUB. The most common endoscopic stigmata seen in MWTs were oozing blood (26 %) or clean base (26 %). Of the patients with MWT, 53 (42 %) received endoscopic therapy. Forty-eight of them (90 %) had epinephrine injections and 25 (48 %) had through-the-scope clips. The rebleeding rate was lower in MWT patients compared with PUB patients (4.9 % vs 12 %, $P=0.016$), but mortality was similar (5.7 vs 7.0 %, $P=0.71$).

Conclusions Although patients presenting with MWT were younger, with a lower rebleeding rate, their mortality was similar to that of patients with PUB. Endoscopic therapy was applied to 42 % MWT patients, with epinephrine injection as the most common modality.

Introduction

Mallory Weiss tear (MWT) is defined by laceration of the mucosa around the esophagogastric junction (OGJ), usually preceded by retching or another cause of rapid increase in intra-abdominal pressure and it has been associated with alcohol intake [1]. It is a relatively uncommon cause of acute upper gastrointestinal bleeding (UGIB), accounting for ≤ 10 % of bleeds on endoscopic examination [2].

MWTs are frequently regarded as mild and self-limiting [3]. However, there is conflicting evidence with regard to mortality associated with MWTs. A European observational study reported that UGIB secondary to MWT and peptic ulcer bleeding (PUB) have similar 30-day mortality rates (5.3 % and 4.6 %, respectively), whereas the last UK audit of UGIB reported a relatively low crude mortality of 3.8 % for MWT compared with 8.9% for PUB [4, 5]. However, a large US database study reported mortality rates as as low as 1.3 % for MWT and 2.0 % for PUB [6].

There also remain unanswered questions regarding the optimal endoscopic management of MWTs. There is uncertainty about which patients with MWTs require endoscopic therapy, with the European Society of Gastrointestinal Endoscopy (ESGE) advising endoscopic therapy only for "actively bleeding" MWTs and the American Society for Gastrointestinal Endoscopy (ASGE) advising it for "ongoing or severe bleeding" [7, 8]. This is different from the accepted definition of high-risk lesions in PUB that require endoscopic therapy, whereby visible vessels (Forrest IIa lesions) are also recommended to have endoscopic therapy (**Supplementary Table 1**) [9]. However, recently published data on 168 patients with MWTs in Korea revealed that the Forrest classification predicted the need for endoscopic therapy with a cut-off between Forrest IIa and IIb lesions (area under the receiver operating curve [AUROC] 0.951, 95 % confidence interval [CI] 0.917–0.985, $P<0.001$). Patients with Forrest Ia, Ib, and IIa lesions required endoscopic treatment, whereas those with Forrest IIb, IIc, and III lesions were successfully managed without endoscopic therapy (sensitivity 95 %; specificity 90.9 %). Furthermore, the receiver operating curve revealed that the Forrest classification predicted recurrent bleeding (defined as verification of bleeding at follow-up endoscopy or fresh hematemesis/melena combined with either shock or a decline of more than 20 g/L in hemoglobin levels within a 24-hour period) fairly well, with a cut-off at Forrest IIa lesions (AUROC 0.723, 95 % CI 0.609–0.836, $P=0.025$) [10].

In addition, the optimal endoscopic treatment modality is unclear. Epinephrine injection, mechanical TTS clips, thermocoagulation, and endoscopic band ligation (EBL) have all been used, with small studies demonstrating safety and efficacy. There remains a lack of clarity about the optimal modality for treating MWTs [11–15]. The UK National Institute for Health and Care Excellence (NICE) guidelines on UGIB did not specify therapy for MWTs, but ASGE suggested that multipolar electrocautery may be the most effective modality and ESGE concluded there is inadequate evidence to indicate a preferred technique but suggested that mechanical modalities (TTS clips and bands) may be superior to epinephrine alone [7, 8, 16].

The aim of our study was to compare patient demographics and outcomes between patients with MWTs and those with PUBs from a large international cohort undergoing endoscopy for UGIB. We also describe the endoscopic stigmata and therapy used in patients with MWTs.

Patients and methods

We prospectively collected data for 1 year on consecutive patients undergoing endoscopy for acute UGIB in six large hospitals across five countries: United Kingdom, United States of America, Denmark, Singapore, and New Zealand. In addition, we collected data on a further consecutive 1-year cohort from two of these centers (Glasgow, UK and Odense, Denmark) and also prospectively collected data on consecutive patients over a 5-year period from Granada, Spain.

Patients were included in the study if they presented to hospital with evidence of UGIB defined by fresh blood hematemesis, coffee-ground vomiting, or melena. Patients who developed UGIB while already inpatients for another reason were not included. We assessed and compared the patients with MWT bleeding and PUB, including baseline demographics, comorbidities, hemodynamic parameters, Forrest classification of endoscopic stigmata, and endoscopic therapy applied. Seven-day rebleeding rates and 30-day mortality rates were compared between the MWT and PUB patient groups, as defined by the endoscopic finding reported at endoscopy.

Statistical methods

Pearsons chi-square test and Fischer's exact test were used to compare proportions. Continuous data were compared using the Mann-Whitney U test. In addition, we estimated the performance of the Forrest classification in predicting rebleeding for MWT or PUB using calculation of AUROCs and 95 % CIs. For this specific analysis, the data for PUB patients were only available from the additional Odense cohort. Data were analyzed using STATA 14.0 (StataCorp, College Station, Texas, United States).

Results

A total of 3648 patients were included in the study (Odense 1162, Glasgow 709, Granada 531, Yale 464 Truro 395, Singapore 324, Dunedin 63). From this cohort, 125 (3.4 %) had MWT-related bleeding and 1140 (31.3 %) had PUB on endoscopy. Patient demographics, symptoms, hemodynamic parameters, and comorbidities are shown in ▶ **Table 1**. The median age of patients with MWT was lower than in those with PUB (61 vs 69 years, $P<0.0001$) and they were more likely to be men (66 % vs 53 %, $P=0.006$). Hematemesis was a more common presenting symptom in those with MWT compared with PUB (71 % vs 24 %, $P<0.001$), whereas melaena was more common in PUB (74 % vs 47 %, $P<0.001$).

Baseline pulse (93 vs 90 bpm, $P=0.039$) and baseline systolic blood pressure (123 vs 117 mm Hg, $p=0.041$) were both higher in patients with MWT compared with PUB. Admission hemoglobin (116 vs 90 g/dL, $P<0.0001$) and albumin (36 vs 34 g/L, $P=$

▶ **Table 1** Comparison of patient characteristics & outcomes between MWT, PUB & all UGIB.

	MWT (n = 125)	PUB (n = 1140)	UGIB overall (n = 3648)	MWT vs. PUB *P*
Age (years, median [95 % CI])	61 [27–86]	69 [37–90]	67 [31–89]	<0.0001
Male sex	83 (66)	606 (53)	2,034 (55.7)	0.006
Symptoms				
▪ Coffee-ground vomiting	23 (23)	228 (25)	810 (26)	0.72
▪ Hematemesis fresh blood	70 (71)	215 (24)	1,164 (37)	<0.001
▪ Melena	59 (47)	845 (74)	2,224 (61)	<0.001
▪ Syncope	10 (11)	158 (18)	283 (12)	0.11
Circulatory parameters (median [range])				
▪ Systolic blood pressure (mm Hg)	123 [75–158]	117 [80–159]	121 [83–164]	0.041
▪ Heart rate (beats/min)	93 [62–137]	90 [61–125]	90 [62–126]	0.039
Blood tests				
▪ Hemoglobin	116 [68–164]	90 [52–138]	101 [55–155]	<0.0001
▪ Urea	12 [2.3–39]	15 [4.5–45]	11 [2.8–41]	0.0019
▪ Albumin	36 [24–46]	34 [22–43]	34 [21–45]	0.0003
Comorbidities				
▪ Ischemic heart disease	26 (21)	275 (24)	780 (21)	0.44
▪ Liver cirrhosis	16 (18)	66 (7.6)	491 (17)	0.002
▪ Any malignancy	11 (8.8)	109 (9.6)	466 (13)	0.87
▪ ASA-score (mean [95 % CI])	2.4 [1–3]	2.5 [1–4]	2.5 [1–4]	0.40
Outcome				
▪ Endoscopic treatment	51 (41)	550 (48)	1,122 (31)	0.13
▪ Rebleeding < 7 days	6 (4.9)	136 (12)	323 (9.2)	0.016
▪ Surgery/embolization	1 (0.8)	23 (2.0)	57 (1.6)	0.50
▪ 30-day mortality	7 (5.7)	78 (7.0)	270 (7.6)	0.71

Numbers are n (%) unless otherwise stated.
MWT, Mallory Weiss tear; PUB, peptic ulcer bleeding; UGIB, upper gastrointestinal bleeding; ASA, American Society of Anesthesiologists; CI, confidence interval.

0.0003) were higher in patients with MWT compared to those with PUB. Liver cirrhosis was present in 16 patients with MWT (18 %) compared to 66 patients with PUB (7.6 %) (P = 0.002). The rates of ischemic heart disease and malignancy were similar between the two groups.

The most common endoscopic stigmata seen in MWTs were oozing blood (Forrest Ib) in 26 %, or a clean base (Forrest III) in 26 %. Patients who had a MWT with spurting hemorrhage (Forrest Ia) had the highest 30-day mortality rate, at 13 % compared to other MWT patients (▶ **Table 2**).

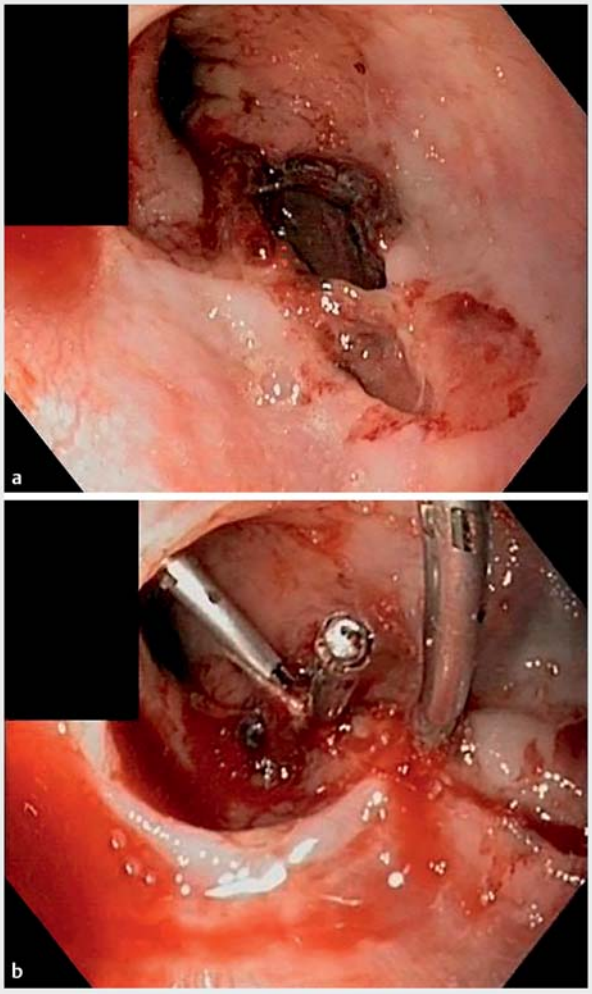
Endoscopic therapy was used to treat 53 MWT patients (42%) and 550 PUB patients (48 %) (P = 0.22). Of the MWT group, 28 (53 %) had endoscopic monotherapy and 25 (47 %) had endoscopic combination therapy. Among patients with MWT who received endotherapy, 48 (90 %) received epinephrine injection (single or combined therapy), 25 (48 %) had through-the-scope (TTS) clips applied (▶ **Fig. 1**), and five (10 %) were treated with thermal ablation. No patient received EBL. Forty-seven percent of MWT patients with adherent clots did not receive endoscopic therapy. Among the 41 patients with actively bleeding MWT, 29 (8/8 Forrest 1a and 21/33 Forrest 1b) received endoscopic therapy. Endoscopic therapy led to initial hemostasis in 28 of 29 patients, with one patient (0.8 %) with MWT not achieving initial hemostasis with endoscopic therapy and requiring surgery. This compared with 23 patients (2 %) with PUB who required embolization or surgery (P = 0.5). The endoscopic therapies used are shown in detail in ▶ **Table 3**.

Rebleeding was significantly less common in MWT patients, seen in six (4.9 %) compared with 136 PUB patients (12 %) (P = 0.016). In MWT patients, the rebleeding rate following endoscopic therapy was 10 % (five of 49, two cases with missing data). None of the eight patients with Forrest 1a MWT rebled.

▶ **Table 2** Stigmata of bleeding using Forrest Classification and outcome among patients with MWTs (n = 117)[1].

Forrest classification	Frequency	Endoscopic therapy	Rebleeding rate	30-day mortality
1a	8 (6.4)	8 (100)	0 (0)	1 (13)
1b	33 (26)	21 (64)	3 (9.4)	1 (3)
2a	4 (3.2)	4 (100)	0 (0)	0 (0)
2b	30 (24)	16 (53)	1 (3.3)	2 (7)
2c	9 (7.2)	2 (22)	1 (11.1)	1 (11)
3	33 (26)	1 (3)	1 (3.0)	2 (6)

MWT, Mallory Weiss tear.
[1] Data missing for eight patients.



▶ **Fig. 1** A middle-aged man was admitted to the hospital with hematemesis and syncope. At endoscopy, a 5 × 15-mm Mallory Weiss tear was identified with an adherent coagulum and oozing bleeding from the lower part of the lesion. The lesion was treated with injection of adrenaline followed by application of TTS clips.

None of the 12 patients with Forrest 1b stigmata (oozing blood) who had not been treated endoscopically rebled. The three Forrest 1b patients who did rebleed had been treated with different endoscopic therapy (epinephrine or TTS clips monotherapy, and combined epinephrine and TTS clips). Among those without active bleeding, rebleeding occurred in one of 23 receiving endoscopic therapy and two of 53 not receiving endoscopic therapy. No patient treated with thermal ablation rebled. The Forrest classification was very poor in predicting rebleeding after MWT: AUROC = 0.56 (95 % CI 0.33–0.79). Thirty-day mortality was similar between the MWT and PUB groups, seen in seven (5.7 %) vs 78 (7.0 %); $P = 0.71$.

Discussion

MWTs are frequently thought to be a relatively benign cause of UGIB compared to other etiologies including PUB. In our international cohort of patients, mortality after bleeding from MWT (5.7 %) was similar to that after PUB (7.0 %), despite the patients being younger and having a lower rebleeding rate. Use of endoscopic therapy was similar in MWT and PUB groups (42 % vs 48%).

Our mortality results are consistent with two other prospective studies. One study from Croatia compared 281 MWT patients with 1530 PUB patients and reported similar 30-day mortality in both groups (5.3 % vs 4.6 %, respectively) [4]. The second study, conducted in Italy, compared 147 MWT patients with 2046 PUB patients, and also reported similar mortality (4.8 % vs 3.9 %) [17]. However, a retrospective study conducted in Japan, to evaluate risk factors for mortality in 93 patients with MWT, reported a mortality rate of 9.7 % [18]. We found that patients with MWT were younger compared to those with PUB. Similar results were seen in the Italian study [17], whereas the Croatian study found no difference in mean patient age between the two groups [4].

Despite the similarity in mortality rates between MWT and PUB in our study, rebleeding rates were significantly higher in those with PUB (12 %) vs MWT (4.9 %, $P = 0.016$). The Croatian study also found higher rebleeding rates in PUB patients (8.4 % vs 1.4 % for MWT) [4], although the Italian study reported 3.8 % rebleeding in both groups [17]. Exact reasons for this are un-

▶ **Table 3** Endoscopic treatment applied in patients undergoing endoscopic treatment for MWT (n = 53 patients).

Endoscopic therapy used	Frequency of use n (%)	[1]Rebleeding rate n (%)
Epinephrine injection only	23 (43)	1 (4)
TTS clips only	4 (8)	1 (25)
Thermal only	1 (2)	0 (0)
Epinephrine injection + TTS clips	21 (40)	2 (10)
Epinephrine injection + Thermal	4 (8)	0 (0)
Endoscopic monotherapy	28 (53)	2 (7)
Endoscopic combination therapy	25 (47)	2 (8)

MWT, Mallory Weiss tear; TTS, through-the-scope.
[1] There were no significant differences between groups.

clear and could be the focus of future studies. A small number of studies have analyzed the risk factors for rebleeding and mortality in patients with MWTs. Presence of shock at presentation and active bleeding at endoscopy were shown to predict recurrent bleeding in MWT [19]. Older age, very low hemoglobin level, elevated aspartate aminotransferase level, and presence of tarry stool were also reported to predict mortality in MWT patients [18].

The optimal endoscopic therapy for MWT remains unclear. A small randomized controlled trial (RCT) from Korea of 34 patients with actively bleeding MWTs compared EBL with endoscopic injections of epinephrine [15]. Primary hemostasis was achieved in all 17 patients in the EBL group and in 16 of 17 patients (94.1 %) in the epinephrine group. No rebleeding or major complication occurred in either group. Observational studies on endoscopic therapy in MWT bleeding have also been reported. Cho et al reported no difference in primary hemostasis or rebleeding when comparing EBL and endoscopic hemoclip placement in 41 patients with UGIB from MWTs [12]. Chung et al compared the injection of hypertonic saline and epinephrine (HSE), endoscopic hemoclip application, or EBL in MWT bleeding [20]. Rebleeding was observed in four of 14 patients treated with HSE injection, with no rebleeding observed in the other two groups. A small RCT from Spain compared endoscopic injection therapy to no endoscopic therapy. Rates of rebleeding (25.8 % vs. 6.2 %, $P<0.05$), length of hospital stay, and transfusion requirements after endoscopy were high in the control group [21]. Finally, Huang et al compared TTS clips and epinephrine injection for actively bleeding MWTs [14]. Primary hemostasis was achieved in all patients and one patient in each group rebled. In a Croatian study, endoscopic TTS clips were applied more frequently than epinephrine injection (54.7 % vs 29.2 %) [4]. The rebleeding rate in that study was not influenced by endoscopic therapy, but mortality was lower in patients who received it ($P<0.001$) [4]. A French study reported a higher rebleeding rate in those treated with combination epinephrine injection and TTS clips, compared with EBL (18 % vs. 0 %, $P=0.02$) [13].

Both the ESGE and ASGE recommend that patients with actively bleeding MWT lesions should receive endoscopic hemostasis [7, 8]. ESGE stated there is currently inadequate evidence to recommend a specific hemostatic modality, but ASGE suggests multipolar electrocoagulation is the most effective therapy for treating bleeding MWT. Despite suggestions that mechanical methods (TTS clips or band ligation) may be more effective than epinephrine injection, this has not been found in all studies [14, 15, 21]. In a randomized sham-controlled prospective trial of multipolar electrocoagulation in non-variceal UGIB, Laine found that this modality had greater hemostatic effect compared with a sham procedure (100 % versus 13 %) in patients with actively bleeding MWT [22].

In our cohort, a similar proportion of patients with MWTs and PUB received endoscopic therapy (42 % v 48 %). Epinephrine injection (single or combined therapy) was used in 90 % patients, with 48 % treated with TTS clips, and thermal ablation used in 10 %. Endoscopic therapy failed to provide hemostasis in only one MWT patient, who required surgery. Almost 50 % MWT patients with an adherent clot were not treated with endotherapy. Rebleeding was less common after MWT compared with PUB.

The Forrest classification was developed more than 40 years ago in an attempt to standardize the characteristics of peptic ulcer disease (**Supplementary Table 1**) [9]. As this classification is commonly used by endoscopists in PUB, it has been suggested it could be used to help guide endoscopic therapy in MWT-related UGIB [10, 23]. A study of 168 patients with MWTs found the Forrest classification was able to predict rebleeding, with an AUROC of 0.723 (95 % CI 0.609–0.836, $P=0.025$) [10]. However, a limitation of the Forrest classification is that stigmata identification and interobserver agreement can be poor [24–26]. We found that the Forrest classification predicted rebleeding after MWT with an AUROC of only 0.56; therefore, our results do not support its use for guiding endoscopic therapy in MWT bleeding.

The strengths of our study include its international multicenter design and the consecutive patients studied. Our sample size is relatively large compared with most previous reports on MWT bleeding. Limitations include the absence of an agreed protocol for endoscopic therapy for MWT related bleeding across all centers, with clinical judgment by the endoscopist

used to guide treatment. However, our data represent real-world clinical practice.

Conclusions

In conclusion, we found that patients presenting with MWT were younger, with a lower rebleeding rate compared with PUB, but the mortality rate was similar in both groups. Endoscopic therapy was applied to 42% of MWT patients, with epinephrine injection, followed by TTS clips, the most common modalities employed. Further RCTs are required to assess the optimal endoscopic therapy for patients with MWTs.

Competing interests

The authors declare that they have no conflict of interest.

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