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Research Article

***Endoscopic nasobiliary drainage comparable with endoscopic biliary stenting
as a preoperative drainage method for malignant hilar biliary
obstruction: A multicenter retrospective study***

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Short Title: ENBD is comparable with EBS

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1 **Abstract**

2 **Introduction:** Preoperative endoscopic biliary drainage (PEBD) for malignant hilar biliary obstruction
3 (MHBO) is widely accepted. Recent PEBD consists of endoscopic nasobiliary drainage (ENBD),
4 conventional endoscopic biliary stenting (CEBS) with plastic stents across the papilla, and endoscopic
5 biliary inside stenting (EBIS) with plastic stents above the papilla, while ENBD is the primary
6 procedure in Asian countries. Thus, we aimed to compare the efficacy of ENBD with those of CEBS
7 and EBIS as a means of PEBD for MHBO.

8 **Methods:** We retrospectively identified patients with MHBO who underwent upfront surgery
9 between January 2011 and December 2018 in a multicenter setting. The outcome measures were
10 cumulative dysfunction of PEBD, risk factors for PEBD dysfunction, and adverse events.

11 **Results:** We analyzed a total of 219 patients, comprising: 163males (74.4%); mean age,
12 69.7(±7.6)years; Bismuth-Corlette classification (BC) I, II, IIIa, IIIb, and IV in 68, 49, 43, 30, and 29
13 patients, respectively; and diagnosis of hilar cholangiocarcinoma and gall bladder cancer in 188 and
14 31 patients, respectively. PEBD procedures were performed in 160 patients with ENBD, 31 patients
15 with CEBS, and 28 patients with EBIS. PEBD dysfunction occurred in 58 patients (26.5%), and the
16 cumulative dysfunction rates were not significantly different among PEBD methods ($P=0.60$).
17 Multivariate analysis showed that BC-IV was significantly associated with the occurrence of PEBD
18 dysfunction (hazard ratio=2.10, $P=0.02$). The adverse event rates were not significantly different
19 among PEBD groups ($P=0.70$).

20 **Conclusion:** ENBD as a means of PEBD for MHBO is comparable with CEBS and EBIS in rates of
21 dysfunction and adverse events.

22

23 Introduction

24 Surgical treatment alone can offer long-term survival in patients with primary malignant hilar biliary
25 obstruction (MHBO), including hilar cholangiocarcinoma and gallbladder cancer [1-3]. Although it
26 remains unclear whether preoperative biliary drainage can reduce morbidity and mortality in
27 patients with MHBO [4, 5], drainage is frequently necessary, following assessment of the surgical
28 resectability and pathological confirmation [6, 7]. Percutaneous transhepatic biliary drainage (PTBD)
29 is not recommended as the first preoperative drainage procedure because of the possibility of tumor
30 seeding and severe complications [8, 9]. Preoperative endoscopic biliary drainage (PEBD) is widely
31 accepted as the standard preoperative biliary drainage technique in Japan [10]. Endoscopic
32 nasobiliary drainage (ENBD) is the primary procedure for PEBD, according to Japanese guidelines [4].
33 Previous studies have reported that ENBD has advantages, including less adverse events, such as
34 tube/stent occlusion with cholangitis, and re-interventions over endoscopic biliary stenting (EBS) as a
35 PEBD method [8, 11]. Currently, ENBD is frequently performed in Japanese high-volume centers [10].
36 However, the method typically involves the external fistula, which has been shown to decrease the
37 quality of life during the preoperative waiting period. In addition, some recent studies have failed to
38 show an advantage of ENBD over EBS as a PEBD method [12-14]. Conventional endoscopic biliary
39 stenting (CEBS) is performed using plastic stents across the major papilla. Meanwhile, recent studies
40 have indicated that novel endoscopic biliary inside stenting (EBIS) is superior to CEBS as a bridging
41 treatment to surgery with plastic stents above the papilla, which was demonstrated in patients with
42 malignant biliary obstruction, including MHBO [15, 16], as well as in patients with unresectable
43 MHBO [16, 17]. However, the most suitable PEBD method remains controversial. Meanwhile,
44 multiple EBD procedures are frequently performed before the final decision on the surgical strategy.
45 It is not known whether the initial EBD method affects tube/stent dysfunction and complications of
46 PEBD at the final decision on the surgical strategy. Furthermore, because of the advent of EBIS and
47 revision of preoperative management protocols in the last decade [10], re-evaluation of the typical
48 PEBD methods that are implemented in surgical care is needed.

49 The aim of this multicenter, retrospective study was to compare ENBD with CEBS and EBIS as a
50 PEBD method in addition to as the initial EBD method and to re-evaluate the usefulness of ENBD for
51 patients with MHBO who underwent upfront radical surgery.

52

53 **Materials and Methods**

54 **Study design**

55 This was a multicenter, retrospective study conducted at Hokkaido University Hospital, Teine-
56 Keijinkai Hospital, Sapporo Medical University, Tonan Hospital, Iwamizawa Municipal General
57 Hospital, NTT East Sapporo Hospital, and Hakodate Municipal Hospital. We retrospectively searched
58 for consecutive patients with MHBO who underwent radical surgical resection between January 2011
59 and December 2018 from the hospital databases. The inclusion criteria were as follows: 1) diagnosis
60 of primary malignant biliary tract cancer based on pathological evidence; 2) main biliary stricture
61 located within 2 cm from the hepatic hilum; 3) history of PEBD until surgery; and 4) patients' or their
62 families' agreement to participate in this study by the opt-out form. The exclusion criteria were as
63 follows: 1) history of PTBD before radical surgery; 2) history of multiple PEBD methods (ENBD + CEBS,
64 ENBD + EBIS, or CEBS + EBIS) as a PEBD method; 3) history of preoperative chemotherapy or
65 radiation therapy for MHBO; 4) history of gastrointestinal tract reconstruction; and 5) refusal to
66 participate in this study by either the patients or their families.

67 We previously conducted a single-center, retrospective study to identify the risk factors for the
68 initial endoscopic procedures for dysfunction of endoscopic biliary drainage (EBD) in preoperative
69 patients with MHBO [14]. Although the inclusion/exclusion criteria and target procedures were
70 different between the previous study and this study, many of the enrolled patients in the previous
71 study were also included in this multicenter, retrospective study.

72 The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (2013
73 revision), as reflected in prior approval by the Human Research Committee of the relevant
74 institutions. This study was approved by the Institutional Review Board at Hokkaido University
75 Hospital (018-0392) and other study institutions and was registered in the UMIN-CTR (clinical trial
76 registration number: UMIN000040605).

77

78 **Endoscopic management for MHBO**

79 Written informed consent was obtained from all patients prior to endoscopic retrograde
80 cholangiography and EBD/PEBD. ENBD tubes or plastic stents were used for the initial EBD (initial
81 ENBD, iENBD/initial CEBS, iCEBS/initial EBIS, iEBIS)/PEBD. In general, the biliary drainage technique
82 for patients with MHBO is single biliary drainage of the future remnant liver lobe. However,

83 additional EBD was performed when cholangitis was suspected in the non-drainage area or when the
84 final decision on the surgical strategy made by the cancer board of each institution required it. ENBD
85 was the first-choice procedure for PEBD in the participating institutions, according to Japanese
86 guidelines [4], except for patients who rejected the procedure or those who were intolerant to ENBD.
87 If the distance from the distal end of the biliary stricture to the sphincter of Oddi was at least 2 cm,
88 EBIS could be selected, as well as ENBD and CEBS. If the preoperative waiting period would be
89 extended at the final decision on the surgical strategy, ENBD could be converted to CEBS/EBIS. Some
90 patients who were referred to the participating institutions for workup of MHBO had undergone
91 CEBS/EBIS previously at other hospitals. The selection of the biliary drainage technique
92 (ENBD/CEBS/EBIS) and endoscopic sphincterotomy were performed at the sole discretion of the
93 endoscopist.

94

95 **Definitions**

96 PEBD was defined as EBD during the preoperative waiting period and divided into three groups:
97 preoperative ENBD (pENBD), preoperative CEBS (pCEBS), and preoperative EBIS (pEBIS). The
98 preoperative waiting period was defined as the duration from the final decision on the surgical
99 strategy by each institutional cancer board for radical surgery (Figure 1). Before PEBD, one or more
100 EBD procedures as re-intervention could be performed to assess the surgical
101 resectability/pathological confirmation, improve cholangitis, or convert from single to multiple biliary
102 drainage due to the final decision on the surgical strategy.

103 PEBD dysfunction was defined as occlusion or dislocation of the ENBD tubes or plastic stents of
104 CEBS/EBIS. Occlusion of an ENBD tube or plastic stent of CEBS/EBIS was defined as follows: 1) acute
105 cholangitis as defined in the Tokyo guideline 2018 [18], and 2) elevation of serum hepatobiliary
106 enzyme levels, any of which can improve after exchange of the tubes/stents. When bile flow in an
107 ENBD tube stopped or extremely decreased, bile reflow after flushing an ENBD tube with
108 physiological saline was not defined as occlusion of an ENBD tube. Dislocation of an ENBD tube or a
109 plastic stent of CEBS/EBIS was defined as dislodgement of the tip of the tubes/stents from the
110 original position to an inappropriate site, as assessed by a roentgenogram. In the present study,
111 removal of an ENBD tube by a patient was defined as the dislocation of an ENBD tube.

112 Functional success was defined as (a) a decrease in serum total bilirubin from >2.0 mg/dL to ≤ 2.0
113 mg/dL, (b) a decrease in serum total bilirubin by half from >2.0 mg/dL, (c) 50% or more decrease in
114 hepatobiliary enzyme levels in the case of serum T-BIL being 2.0 mg/dL or less within 14 days after

115 biliary drainage, or (d) no increase in serum total bilirubin > 2.0 mg/dL and of hepatobiliary enzymes
116 in the case of biliary decompression previously.

117 In the present study, the type of hilar biliary obstruction in patients with gallbladder cancer, as
118 well as that in patients with hilar cholangiocarcinoma, was classified according to the Bismuth-
119 Corlette grade (BC).

120 Regarding adverse events, contralateral segmental cholangitis was defined as cholangitis that
121 occurred in an undrained area. When contralateral segmental cholangitis occurred, an additional
122 ENBD tube or plastic stent of CEBS/EBIS was placed in the undrained area. In this study, contralateral
123 segmental cholangitis was regarded as an adverse event because it is mainly caused by tumor-related
124 obstruction. Ipsilateral segmental cholangitis was defined as cholangitis that occurred in the same
125 lobe as the drained area and improved with conservative treatment. Pancreatitis, bleeding, and
126 perforation related to the endoscopic biliary stenting/tubing procedure, and their severity was
127 defined according to the American Society for Gastrointestinal Endoscopy lexicon [19]. Acute
128 cholecystitis and cholangitis were defined according to the 2018 Tokyo guidelines [20].

129

130 **Outcome measures**

131 The primary outcome measure of the present study was the cumulative dysfunction of PEBD
132 according to the PEBD method. The secondary outcomes measures were functional success, details
133 of PEBD duration and dysfunction, and risk factors for PEBD dysfunction: age (<75 or ≥75 year); sex
134 (male or female); final diagnosis (cholangiocarcinoma or gallbladder cancer); BC grade (I, II, IIIa, IIIb,
135 or IV); cholangitis before PEBD (presence or absence); pancreatitis due to EBD/PEBD procedures
136 (presence or absence); biliary drainage method (ENBD, CEBS, or EBIS); number of intubated PEBD
137 tubes/stents (single or multiple); diameter of the largest PEBD tube/stent (≤6-Fr or ≥7-Fr); type of
138 PEBD tubes/stents (straight or pigtail); endoscopic sphincterotomy (presence or absence);
139 preoperative waiting period (≤40 days or >40 days); and percutaneous transhepatic portal vein
140 embolization (PTPE) before surgery (presence or absence) were used as covariates. Adverse events
141 associated with PEBD were also analyzed.

142

143 **Statistical analysis**

144 Statistical analysis was performed using the free software EZR [21]. Results are shown as means
145 (standard deviation) for quantitative variables, medians (interquartile range) for nonparametric

146 variables, and percentages for categorical variables. A one-way ANOVA was conducted to compare
147 continuous variables among the PEBD methods. The Kruskal–Wallis test was conducted to compare
148 the median values of the preoperative waiting period among the PEBD methods. Categorical
149 variables were compared using the chi-squared test or Fisher’s exact test, as appropriate. The
150 cumulative incidences of PEBD dysfunction were estimated using the Kaplan–Meier method, and the
151 differences among PEBD methods were evaluated using the log-rank test. Patients who underwent
152 radical surgical resection, re-intervention, or conversion to another EBD method without dysfunction
153 of PEBD or drainage-related adverse events were regarded as censored. The risk factors for PEBD
154 dysfunction were analyzed using the Cox proportional hazards model. Factors with a *P*-value < 0.20 in
155 the univariate analysis, were included in the multivariate analysis. Differences were considered
156 statistically significant at *P* < 0.05.

157

158 **Results**

159 **Baseline characteristics**

160 The database searched for the retrieval of 219 consecutive patients who were finally analyzed in the
161 present study (Figure 2). The baseline characteristics of the patients are shown in Table 1. The
162 patients included 163 men and 56 women, with a mean age of 69.7 (± 7.6) years. The final diagnoses
163 were cholangiocarcinoma in 188 patients and gallbladder cancer in 31 patients. The BC grades were
164 as follows: I, 68; II, 49; IIIa, 43; IIIb, 30; and IV, 29. ENBD, CEBS, and EBIS were performed using the
165 PEBD method in 160 (pENBD), 31 (pCEBS), and 28 patients (pEBIS), respectively. A total of 157
166 patients (71.7%) had undergone one or more EBDs before PEBD. There were no significant
167 differences in the percentage of patients who underwent one or more EBD procedures before PEBD
168 (multiple EBD procedures) among the three groups (pENBD: 68.1% vs. pCEBS: 74.2% vs. pEBIS: 89.3%,
169 *P* = 0.06). The incidence rates of cholangitis before PEBD in the pENBD, pCEBS, and pEBIS groups
170 were 23.1%, 16.1%, and 25.0%, respectively, and were not significantly different among the PEBD
171 groups (*P* = 0.70).

172 The initial EBD methods were ENBD in 159 patients (iENBD), CEBS in 52 patients (iCEBS), and
173 EBIS in 8 patients (iEBIS). A flowchart of the initial EBD method for PEBD is shown in Figure 3. The
174 main reasons for the additional EBD are listed in Table 2.

175 The functional success rates of PEBD in the pENBD, pCESB, and pEBIS groups were 100%
176 (160/160), 100% (31/31), and 100% (28/28), respectively. All patients underwent radical surgical
177 resection as scheduled. The median preoperative waiting period of the entire cohort was 41 days

178 (interquartile range, 26–56) and was not significantly different among the PEBD groups ($P = 0.55$).
179 The rates of endoscopic sphincterotomy at PEBD were 53.1%, 45.2%, and 39.3% in the pENBD,
180 pCEBS, and pEBIS groups, respectively, and were not significantly different among the groups ($P =$
181 0.32). Details of the PEBD status and radical surgical resection are shown in Table 3.

182

183 **Primary outcome**

184 The median follow-up durations (interquartile range) of PEBD in the pENBD, pCEBS, and pEBIS groups
185 were 30.5 days (14–47), 23.0 days (14–49), and 24.0 days (8–42), respectively, and were not
186 significantly different among them ($P = 0.54$). Dysfunction of PEBD occurred in 58 patients (26.5%),
187 among whom occlusion and stent migration occurred in 34 and 24 patients, respectively. The
188 cumulative dysfunction rates of PEBD in all patients were 23.8%, 37.4%, and 41.3% at 30, 60, and 90
189 days, respectively (Figure 4A). The dysfunction rates of PEBD in the pENBD, pCEBS, and pEBIS groups
190 were 25.0% (40/160), 35.5% (11/31), and 24.1% (7/28), respectively ($P = 0.45$). The cumulative
191 dysfunction rates of PEBD were not significantly different among the PEBD methods ($P = 0.60$) (Figure
192 4B).

193 We also analyzed the patients according to the initial EBD method, to identify the effect of the
194 initial EBD method on the dysfunction of PEBD. The dysfunction rates of the iENBD, iCEBS, and iEBIS
195 groups during the preoperative period were 26.4% (42/159), 28.8% (15/52), and 12.5% (1/8),
196 respectively, and were not significantly different among the groups ($P = 0.77$). The cumulative
197 dysfunction rates of PEBD were also not significantly different among the groups ($P = 0.65$).

198

199 **Secondary outcomes**

200 **Details of outcomes of PEBD**

201 After PEBD, 137 patients (62.6%) underwent radical surgical resection without re-intervention.
202 Dysfunction of PEBD occurred in 58 patients (26.4%). The remaining 24 patients (11.0%) underwent
203 re-intervention for the following reasons: contralateral segmental cholangitis in 11 patients,
204 conversion to another EBD method without dysfunction of PEBD in 6 patients (conversion from
205 external to internal drainage by patient requirement in 2 patients, and from internal to external
206 drainage for bile monitoring in 4 patients); preventive tube exchange due to slight tube dislocation
207 on roentgenogram in 5 patients; pancreatitis due to compression of the pancreatic duct by the ENBD
208 tube in 1 patient, and bleeding after endoscopic sphincterotomy in 1 patient.

209

210 **Risk factors of PEBD dysfunction**

211 We performed a univariate analysis of patient characteristics and PEBD procedures related to
212 dysfunction (Table 4). The PEBD dysfunction rates were significantly different between BC classes (I,
213 II, IIIa, and IIIb vs. IV) ($P = 0.01$). The results of the multivariate analysis showed that BC-IV was an
214 independent predictive factor for PEBD dysfunction (hazard ratio = 2.01, $P = 0.02$).

215 There were significant differences in the distributions of BC grades among the three PEBD
216 methods ($P < 0.01$). Therefore, we also evaluated the predictive factors for PEBD dysfunction in
217 patients with BC-IIIa, IIIb, and IV (Table 5). Multivariate analysis revealed that the hazard ratio was
218 higher in the CEBS group (hazard ratio = 2.51, $P = 0.04$). BC-IV was also an independent predictive
219 factor for PEBD dysfunction (hazard ratio = 2.54, $P = 0.02$).

220

221 **Adverse events of PEBD**

222 During the study period, 42 patients (19.2%) experienced 42 adverse events (Table 6). The adverse
223 event rates were 20.6% (33/160), 12.9% (4/31), and 17.9% (5/28) in the pENBD, pCEBS, and pEBIS
224 groups, respectively, and were not significantly different among the PEBD groups ($P = 0.70$). No
225 severe adverse events were observed in this study. The incidence rates of contralateral segmental
226 cholangitis and ipsilateral segmental cholangitis were not significantly different among the PEBD
227 groups. Pancreatitis occurred in 16 patients. One of these 16 patients had moderate pancreatitis due
228 to compression of the pancreatic duct by the ENBD tube 21 days after PEBD, and the event was
229 successfully treated by the addition of endoscopic nasopancreatic drainage. Acute cholecystitis
230 occurred in three patients (moderate in two patients and mild in one patient). One patient with
231 moderate cholecystitis underwent percutaneous transhepatic gallbladder drainage, whereas the
232 remaining two patients with cholecystitis were successfully treated with conservative therapy.
233 Bleeding after endoscopic sphincterotomy occurred in one patient undergoing ENBD; the patient was
234 successfully treated with endoscopic hemostasis, and the ENBD tube was replaced.

235

236 **Comparison between the ENBD and EBS (CEBS/EBIS) groups**

237 We also evaluated the baseline characteristics of the patients, details of PEBD procedures,
238 dysfunctions of PEBD, and rates of adverse events between the pENBD and preoperative EBS (pEBS)
239 (pCEBS/pEBIS) groups. The BC grades in the pENBD group were as follows: I in 44 patients (27.5%), II

240 in 42 patients (26.3%), IIIa in 28 patients (17.5%), IIIb in 24 patients (15.0%), and IV in 22 patients
241 (13.7%); and in the pEBS group, I was present in 24 patients (40.7%), II in 7 patients (11.9%), IIIa in 15
242 patients (25.4%), IIIb in 6 patients (10.2%), and IV in 7 patients (11.8%). The distribution of BC grades
243 was not significantly different between the two groups ($P = 0.07$). The sizes of ENBD tubes were 5-Fr
244 in 81 patients (50.6%) and ≥ 6 -Fr in 79 patients (49.4%) in the pENBD group, and those of the largest
245 stents were 5-Fr in 4 patients (6.8%) and ≥ 6 -Fr in 55 patients (93.2%) in the pEBS group ($P < 0.01$).
246 The two groups did not differ significantly in terms of other baseline characteristics and PEBD
247 procedures. The dysfunction rates of PEBD in the pENBD and pEBS groups were 25.0% (40/160) and
248 30.5% (18/59), respectively ($P = 0.49$). The cumulative dysfunction rates of PEBD were not
249 significantly different between the pENBD and pEBS groups ($P = 0.37$) (Figure 5). The adverse event
250 rates in the pENBD and pEBS groups were 20.6% (33/160) and 15.3% (9/59), respectively, and were
251 not significantly different between the two groups ($P = 0.44$).

252

253 **Discussion/Conclusion**

254 The present study revealed that ENBD was comparable with CEBS and EBIS in terms of the rates of
255 PEBD dysfunction or adverse events in patients with MHBO. Although previous studies have reported
256 that ENBD has advantages over CEBS as a PEBD method in terms of adverse events, including
257 tube/stent occlusion with cholangitis and re-interventions [8, 11], more recent studies have shown
258 that there were no significant differences between ENBD and CEBS [12-14], as well as the present
259 study. The advantages of ENBD are the ability to monitor bile quality and output and to perform
260 preoperative cholangiography via a drainage tube, while the disadvantage of the method is
261 nasopharyngeal discomfort. The advantages and disadvantages of CEBS and EBIS are completely
262 opposite to those of ENBD; therefore, any PEBD method can be selected for different purposes in
263 cases with short preoperative periods. However, EBS, especially EBIS, should be selected in cases
264 with long preoperative periods in order to prevent a decline in quality of life. Meanwhile, the sub-
265 analysis of the present study in patients with BC-III and IV indicated that CEBS would have a high
266 incidence of PEBD dysfunction, as well as a previous study [8].

267 To date, few previous studies have focused on the efficacy of EBIS as a PEBD method in patients
268 with MHBO who underwent upfront radical surgery. A previous retrospective study in preoperative
269 patients with malignant biliary strictures showed that the average stent patency was significantly
270 longer in the EBIS group than in the CEBS group (85.2 versus 49.1 days, $P < 0.05$) [15]. However, the
271 study included patients with distal biliary stricture in addition to MHBO, as well as those who
272 received neoadjuvant therapy. Other previous studies in patients with unresectable MHBO have also

273 revealed that stent patency in the EBIS group was significantly longer than that in the CEBS group
274 [16, 17]. Therefore, we hypothesized that the cumulative dysfunction rate of PEBD for MHBO in the
275 EBIS group was lower than that in the CEBS group. Recently, a single-center, retrospective study
276 revealed that EBIS was a possible alternative to ENBD as a bridge to a definitive operation for
277 patients with resectable MHBO [22]. Thus, further prospective studies with a larger cohort are
278 needed to accurately compare these PEBD methods for patients with MHBO.

279 In the multivariate analysis of risk factors for dysfunction of PEBD, BC-IV was found to be an
280 independent predictive factor, which can be explained by the fact that the bile ducts for PEBD in BC-
281 IV cases are the 2nd/3rd branch duct and are narrower than those in BC-I-III, as previously described
282 [14]. Therefore, patients with BC-IV should undergo radical surgical resection as early as possible. In
283 addition, because PEBD for MHBO, especially BC-IV MHBO, is occasionally technically difficult, PTBD
284 should also be considered.

285 There are several limitations to the present study. First, this was a retrospective, non-
286 randomized study. Second, selection bias could not be fully avoided because there were few
287 differences among the participating institutions regarding the selection of the PEBD method,
288 assessment of resectability, and the final operative strategy. Third, this study included patients with
289 MHBO who underwent radical surgery (per-protocol analysis), but not all patients with MHBO who
290 would be candidates for radical surgery (intention-to-treat analysis). Our per-protocol analysis could
291 not accurately determine the technical success rate in clinical practice. Fourth, patients who received
292 neoadjuvant therapy were excluded from this study. If neoadjuvant therapy is selected, the
293 preoperative waiting period is extended compared to that in the case of upfront surgery, and the
294 results may differ according to the treatment strategy. Finally, we did not obtain postoperative
295 parameters, such as liver failure and complications, in this study. Future studies should include these
296 parameters to evaluate the postoperative survival times.

297 In conclusion, ENBD is comparable with CEBS and EBIS in patients with MHBO who undergo
298 upfront radical surgery. However, further prospective studies with larger cohorts are needed to
299 accurately compare these PEBD methods for patients with MHBO.

300

301 **Statements**

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308 Hepatology, Hakodate Municipal Hospital) for collecting the data.

309

310 **Statement of Ethics**

311 Study approval statement: This study protocol conformed to the ethical guidelines of the 1975
312 Declaration of Helsinki (2013 revision), as reflected in prior approval by the Human Research
313 Committee of the relevant institutions. This study was approved by the Institutional Review Board at
314 Hokkaido University Hospital (018-0392) and other study institutions, and was registered in UMIN-
315 CTR (clinical trial registration number: UMIN000040605).

316 Consent to participate statement: This study was a retrospective observational study and did not
317 necessarily require written informed consent because it was a study that used only information such
318 as medical records without using samples. Informed consent to participate in the study was obtained
319 from the patients or their families using an opt-out form.

320

321 **Conflict of Interest Statement**

322 Author A.K. has received consultant fee from Gadelius Medical and lecture fee from Olympus
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324

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327

328 **Author Contributions**

329 R.S. designed the research, performed the research (data acquisition and data analysis), and wrote
330 the manuscript; M.K. performed the research (data analysis) and wrote the manuscript and critical
331 revision; T.H., M.Y., H.I., H.Y., and M.O. performed the research (data acquisition) and critically
332 reviewed the manuscript; A.K. supervised the entire research; all authors read and approved the final
333 manuscript.

334

335 **Data Availability Statement**

336 The data that support the findings of this study are not publicly available due to their containing
337 information that could compromise the privacy of research participants but are available from the
338 corresponding author M.K.

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Figure Legends

Figure 1.

Definition of preoperative endoscopic biliary drainage (PEBD) and preoperative waiting period in the present study

EBD, endoscopic biliary drainage; MHBO, malignant hilar biliary obstruction; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage

Figure 2.

Flow chart of the present study

EBD, endoscopic biliary drainage; GI, gastrointestinal; MHBO, malignant hilar biliary obstruction; NAC, neoadjuvant chemotherapy; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage; PTBD, percutaneous transhepatic biliary drainage.

Figure 3.

Flow chart of convert of EBD method to PEBD

CEBS, conventional endoscopic biliary stenting; EBD, endoscopic biliary drainage; EBIS, endoscopic biliary inside stenting; ENBD, endoscopic nasobiliary drainage; iCEBS, initial conventional endoscopic biliary stenting; iEBIS, initial endoscopic biliary inside stenting; iENBD, initial endoscopic nasobiliary drainage; pCEBS, preoperative conventional endoscopic biliary stenting; PEBD, preoperative endoscopic biliary drainage; pEBIS, preoperative endoscopic biliary inside stenting; pENBD, preoperative endoscopic nasobiliary drainage.

Figure 4.

(A) Cumulative incidence of preoperative endoscopic biliary drainage (PEBD) dysfunction.

(B) Cumulative incidence of PEBD according to the PEBD method (pENBD/pCEBS/pEBIS). The cumulative dysfunction rates of PEBD were not significantly different among the PEBD methods ($P = 0.60$).

Figure 5.

Cumulative incidence of preoperative endoscopic biliary drainage (PEBD) dysfunction according to the PEBD method (pENBD and pEBS [pCEBS/pEBIS]). The cumulative dysfunction rates of PEBD were not significantly different between the pENBD and pEBS groups ($P = 0.37$).

Tables

Table 1. Baseline characteristics of patients

	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	P-value
Age, mean (\pm SD), years	69.7 (\pm 7.6)	69.2 (\pm 7.4)	71.7 (\pm 7.4)	70.3 (\pm 8.5)	0.23
Sex, n (%)					0.56
Male	163 (74.4)	116 (72.5)	24 (77.4)	23 (82.1)	
Female	56 (25.6)	44 (27.5)	7 (22.6)	5 (17.9)	
Final diagnosis, n (%)					0.82
Cholangiocarcinoma	188 (85.8)	136 (85.0)	27 (87.1)	25 (89.3)	
Gallbladder cancer	31 (14.2)	24 (15.0)	4 (12.9)	3(10.7)	
Bismuth-Corlette classification, n (%)					< 0.01
I	68 (31.1)	44 (27.5)	16 (48.5)	8 (28.6)	
II	49 (22.4)	42 (26.2)	5 (15.1)	2 (7.1)	
IIIa	43 (19.6)	28 (17.5)	6 (18.2)	9 (32.2)	
IIIb	30 (13.7)	4 (15.0)	4 (12.1)	2 (7.1)	
IV	29 (13.2)	22 (13.8)	0	7 (25.0)	
Cholangitis before PEBD, n (%)					0.70
	49 (22.4)	37 (23.1)	5 (16.1)	7 (25.0)	
Pancreatitis due to EBD/PEBD procedures, n (%)					0.64
	37 (16.9)	26 (16.3)	7 (22.6)	4 (14.3)	
Initial EBD method, n (%)					< 0.01
iENBD	159 (72.6)	127 (79.4)	15 (48.4)	17 (60.7)	
iCEBS	52 (23.7)	31 (19.4)	16 (51.6)	5 (17.9)	
iEBIS	8 (3.7)	2 (1.2)	0	6 (21.4)	
One or more re-intervention by EBD before PEBD, n (%)					

157 (71.7)

109 (68.1)

23 (74.2)

25 (89.3)

0.06

EBD: Endoscopic biliary drainage, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 2. Details of endoscopic biliary drainage (EBD) before preoperative EBD (PEBD)

	All (n = 219)	iENBD (n = 159)	iCEBS (n = 52)	iEBIS (n = 8)	P-value
No re-intervention, n (%)	62 (28.3)	51 (32.1)	8 (15.4)	3 (37.5)	0.04
One or more re-intervention by EBD before PEBD, n (%)	157 (71.7)	108 (67.9)	44 (84.6)	5 (62.5)	
Main reason of the additional EBD, n (%) (n=157)					< 0.01
Re-biopsy	82 (52.2)	55 (50.9)	24 (54.5)	3 (60.0)	
Tube/stent dysfunction	30 (19.1)	19 (17.6)	11 (25.0)	0	
Conversion from iENBD to CEBS/EBIS for quality of life improvement	22 (14.0)	22 (20.4)	0	0	
Conversion from single to multiple biliary drainage due to the surgical strategy	10 (6.4)	9 (8.3)	1 (2.3)	0	
Conversion from iCEBS/iEBIS to ENBD to monitor bile output or to perform cholangiography via ENBD tube	9 (5.7)	0	7 (15.9)	2 (40.0)	
Adverse event related to the initial EBD procedure	4 (2.6)	3 (2.8)	1 (2.3)	0	

CEBS: conventional endoscopic biliary stenting, EBD: Endoscopic biliary drainage, EBIS: endoscopic biliary inside stenting, ENBD: endoscopic nasobiliary drainage, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 3. Details of preoperative endoscopic biliary drainage (PEBD) and radical surgical resection

	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	P-value
Preoperative waiting period, median (interquartile range), days					
	41 (26–56)	41 (26–55)	43 (22–61)	40 (26–58)	0.55
Number of the PEBD tubes, n (%)					0.19
Single	188 (85.8)	109 (68.1)	26 (83.9)	21 (75.0)	
Multiple	63 (28.8)	51 (31.9)	5 (16.1)	7 (25.0)	
Size of the largest PEBD tube/stent, n (%)					< 0.01
5-Fr	85 (38.8)	81 (50.6)	1 (3.2)	3 (10.7)	
6-Fr	70 (32.0)	68 (42.5)	1 (3.2)	1 (3.6)	
≥ 7-Fr	64 (29.2)	11 (6.9)	29 (93.6)	24 (85.7)	
Type of PEBD tubes/stents, n (%)					0.17
Straight	186 (84.9)	132 (82.5)	27 (87.1)	27 (96.4)	
Pigtail	33 (15.1)	28 (17.5)	4 (12.9)	1 (3.6)	
History of endoscopic sphincterotomy at PEBD, n (%)					0.32
	110 (50.2)	85 (53.1)	14 (45.2)	11 (39.3)	
Percutaneous transhepatic portal vein embolization until surgery, n (%)					0.01
	129 (58.9)	98 (61.3)	11 (35.5)	20 (71.4)	
Surgical procedure, n (%)					< 0.01
Bile duct resection (+ hepatectomy of segment 4a/5)					
	13 (6.0)	8 (5.0)	5 (16.1)	0	
Hilar resection + pancreatoduodenectomy					
	22 (10.0)	11 (6.9)	8 (25.8)	3 (10.7)	
Left hepatectomy/left hepatic trisegmentectomy					
	55 (25.1)	42 (26.2)	6 (19.4)	7 (25.0)	

Right hepatectomy/right hepatic trisegmentectomy

97 (44.3) 75 (46.9) 7 (22.6) 15 (53.6)

Hepatectomy/hepatic trisegmentectomy + pancreatoduodenectomy

32 (14.6) 24 (15.0) 5 (16.1) 3 (10.7)

pCEBS: Preoperative conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS:

Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Table 4. Univariate and multivariate analyses of risk factors for dysfunction of preoperative endoscopic biliary drainage (PEBD)

	Univariate analysis		Multivariate analysis		
	n	P-value	Hazard ratio	95%CI	P-value
Age		0.20			
< 75 years	161				
≥ 75 years	58				
Sex		0.97			
Male	163				
Female	56				
Final diagnosis		0.93			
Cholangiocarcinoma	188				
Gallbladder cancer	31				
Bismuth-Corlette classification		0.01			
I/II/IIIa/IIIb	190		1		
IV	29		2.10	1.12–3.93	0.02
Cholangitis before PEBD		0.26			
Absence	170				
Presence	49				
Pancreatitis due to EBD/PEBD procedures		0.26			
Absence	182				
Presence	37				
Initial EBD method		0.66			
iENBD	159				
iCEBS	52				

iEBIS	8				
PEBD method		0.60			
pENBD	160				
pCEBS	31				
pEBIS	28				
Number of PEBD tubes/stents		0.79			
Single	156				
Multiple	63				
Size of the largest PEBD tube/stent		0.18			
5-Fr	85		1		
≥ 6-Fr	134		0.76	0.45–1.30	0.32
Type of PEBD tubes/stents		0.88			
Straight	186				
Pigtail	33				
History of endoscopic sphincterotomy		0.30			
Absence	109				
Presence	110				
Preoperative waiting period		0.77			
≤ 40 days	105				
> 40 days	114				
PTPE until surgery		0.60			
Absence	90				
Presence	129				

CI: Confidential interval, EBD: Endoscopic biliary drainage, iCEBS: Initial conventional endoscopic biliary stenting,

iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative

conventional endoscopic biliary stenting, PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage, PTPE: Percutaneous transhepatic portal vein embolization

Table 5. Univariate and multivariate analyses of risk factors for dysfunction of preoperative endoscopic biliary drainage (PEBD) in patients with Bismuth-Corlette classification (BC) IIIa, IIIb, and IV

	Univariate analysis		Multivariate analysis		
	n	P-value	Hazard ratio	95%CI	P-value
Age		0.60			
< 75 years	79				
≥ 75 years	23				
Sex		0.35			
Male	74				
Female	28				
Final diagnosis		0.71			
Cholangiocarcinoma	90				
Gallbladder cancer	12				
Bismuth-Corlette classification		0.15			
IIIa/IIIb	73		1		
IV	29		2.54	1.17–5.50	0.02
Cholangitis before PEBD		0.89			
Absence	84				
Presence	18				
Pancreatitis due to EBD/PEBD procedures		0.31			
Absence	81				
Presence	21				
Initial EBD method		0.89			
iENBD	74				
iCEBS	23				

iEBIS	5				
PEBD method		0.13			
pENBD	74		1		
pCEBS	10		2.51	1.01–6.25	0.04
pEBIS	18		0.36	0.10–1.21	0.10
Number of PEBD tubes/stents		0.62			
Single	60				
Multiple	42				
Size of the largest PEBD tube/stent		0.65			
5-Fr	51				
≥ 6-Fr	51				
Type of PEBD tubes/stents		0.58			
Straight	88				
Pigtail	14				
History of endoscopic sphincterotomy		0.31			
Absence	51				
Presence	51				
Preoperative waiting period		0.80			
≤ 40 days	51				
> 40 days	51				
PTPE until surgery		0.60			
Absence	42				
Presence	60				

CI: Confidential interval, iCEBS: Initial conventional endoscopic biliary stenting, iEBIS: Initial endoscopic biliary inside stenting, iENBD: Initial endoscopic nasobiliary drainage, pCEBS: Preoperative conventional endoscopic biliary stenting,

PEBD: Preoperative endoscopic biliary drainage, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage, PTPE: Percutaneous transhepatic portal vein embolization

Table 6. Adverse events of preoperative endoscopic biliary drainage (PEBD)

	All (n = 219)	pENBD (n = 160)	pCEBS (n = 31)	pEBIS (n = 28)	P-value
All adverse event, n (%)	42 (19.2)	33 (20.6)	4 (12.9)	5 (17.9)	0.70
Severe/moderate/mild, n	0/24/18	0/20/13	0/3/1	0/1/4	0.22
Contralateral segmental cholangitis, n (%)					
	11 (5.0)	10 (6.3)	0	1 (3.6)	0.47
Ipsilateral segmental cholangitis without re-intervention, n (%)					
	10 (4.6)	6 (3.8)	1 (3.2)	3 (11.1)	0.22
Pancreatitis, n (%)	16 (7.3)	14 (8.8)	1 (3.2)	1 (3.6)	0.57
Cholecystitis, n (%)	3 (1.4)	2 (1.3)	1 (3.2)	0	0.61
Bleeding, n (%)	1 (0.5)	1 (0.6)	0	0	1

pCEBS: Preoperative conventional endoscopic biliary stenting, pEBIS: Preoperative Initial endoscopic biliary inside stenting, pENBD: preoperative endoscopic nasobiliary drainage

Diagnosis of MHBO by CT images and biopsies
with/without EBD

Inoperable

Final decision of surgical strategy

PEBD

pENBD

pCEBS

pEBIS

Radical surgery

Preoperative waiting period

Search of database for
patients with EBD for MHBO and radical resection: 251

Exclusion: 32
PTBD 11, multiple PEBD 10,
No drainage 8, NAC 2,
GI tract reconstruction 1

Patients with PEBD: 219

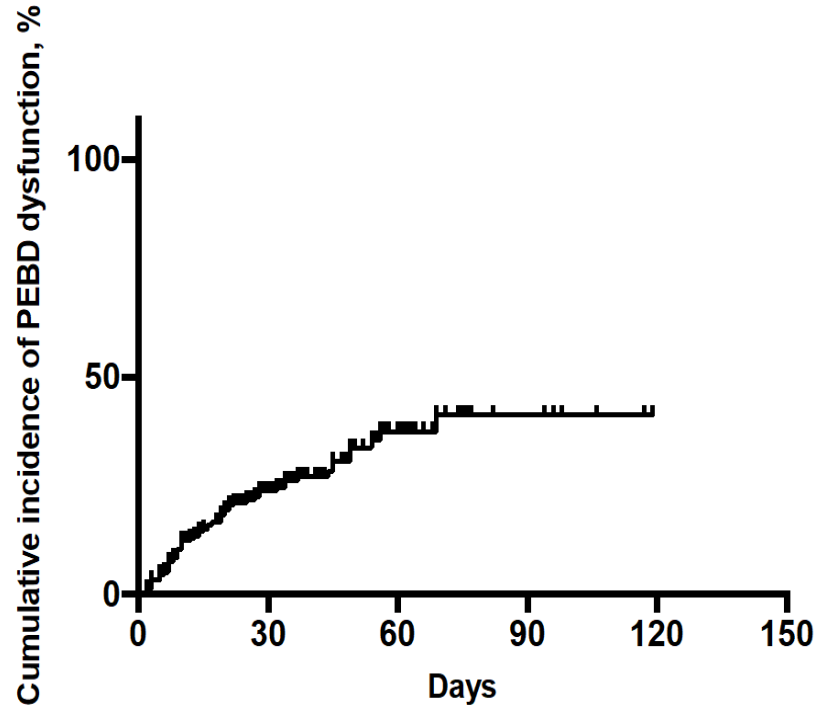
pENBD: 160

pCEBS: 31

pEBIS: 28

Analysis of clinical outcomes

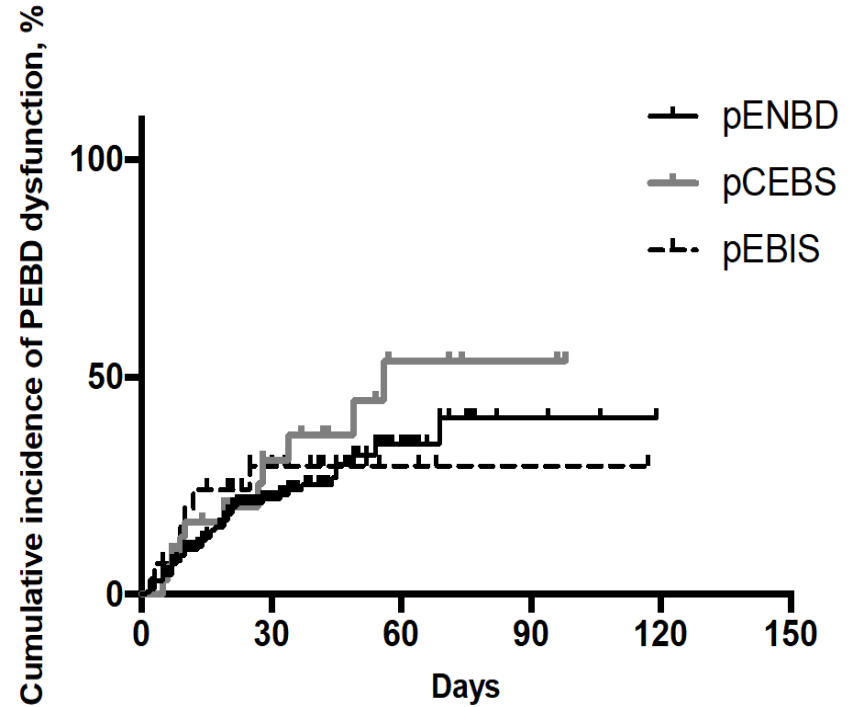
(A)



Number at risk

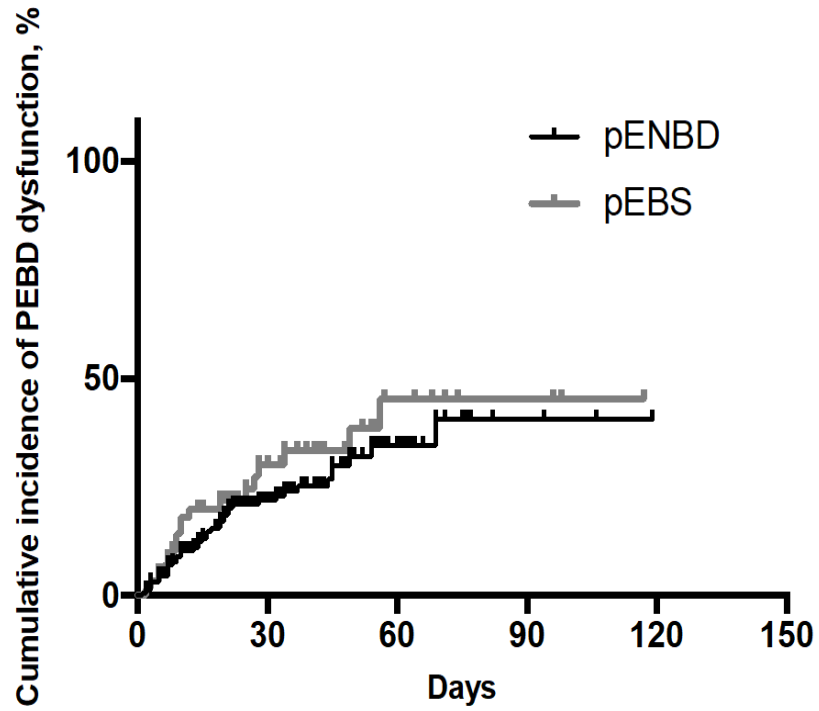
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(B)



Number at risk

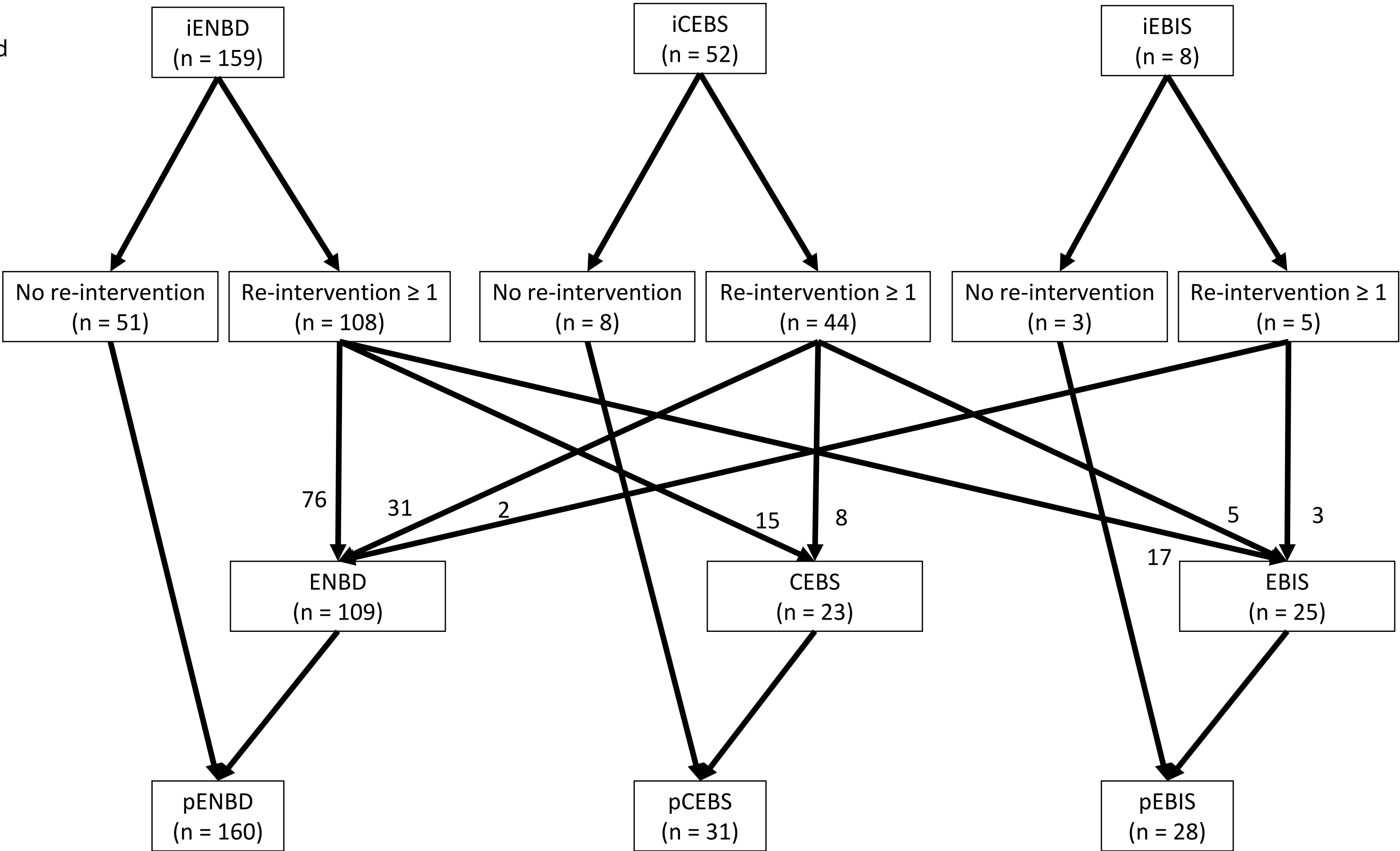
pENBD	160	81	19	3	0
pCEBS	31	12	4	2	0
pEBIS	28	12	3	1	0



Number at risk

pENBD	160	81	19	3	0
pEBS	59	24	7	3	0

Initial EBD method



PEBD method