Digestive Endoscopy 2022; **34**: 1459–1470 doi: 10.1111/den.14354

Original Article

Nomogram for prediction of adverse events after lumen-apposing metal stent placement for drainage of pancreatic fluid collections

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Objectives: To generate a prognostic model based on a nomogram for adverse event (AE) prediction after lumen-apposing metal stents (LAMS) placement in patients with pancreatic fluid collections (PFC).

Methods: Data from a large multicenter series of PFCs treated with LAMS placement were retrieved. AE (overall and excluding mild events) prediction was calculated through a logistic regression model and a nomogram was created and internally validated after bootstrapping. Results were expressed in terms of odds ratio (OR) and 95% confidence interval (CI). Discrimination was assessed by c-statistics and calibrated by comparing deciles of predicted and observed ORs.

Results: Overall, 516 patients were included (males 68%, mean age 61.6 ± 15.2 years). PFCs were predominantly walled-off necrosis (52.1%). Independent predictors of AE occurrence were injury of main pancreatic duct (OR in the case of leak 2.51, 95% CI 1.06–5.97, $P = 0.03$; OR in the case of complete disruption 2.61, 1.53–4.45, $P = 0.01$), abnormal vessels (OR in the case of perigastric varices 2.90, 1.31–6.42, $P = 0.008$; OR in the case of pseudoaneurysm 2.99, 1.75–11.93, $P = 0.002$), using a multigate technique (OR 3.00, 1.28–5.24; $P = 0.05$), and need of percutaneous drainage (OR 2.81, 1.03–7.65, $P = 0.04$). By nomogram, a score beyond 200 points corresponded to a 50% probability of AE occurrence. The model was confirmed even when excluding mild AEs and it showed optimal discrimination (c-index 76.8%, 95% CI 74–79), confirmed after internal validation.

Conclusion: Patients with preprocedural evidence of pancreatic duct leak/disruption, vessel alteration, requiring percutaneous drainage or a multigate technique are at higher risk for AE.

Key words: complication, LAMS, predictive model, pseudocyst, walled-off necrosis

INTRODUCTION

LUMEN-APPOSING METAL STENTS (LAMS) and double pigtail plastic stents (DPPS) represent valuable therapeutic options for the drainage of pancreatic fluid collections (PFC). Due to the large stent diameter, LAMS have been found to be very effective at draining pancreatic pseudocysts (PPs) and walled-off necrosis (WON) with resolution of PFCs.[1] The design of the stent, particularly its biflanged ends, for LAMS appear to prevent the risk of stent migration according to retrospective cohort studies,[2,3] However, a recent systematic review and meta-analysis showed conflicting results in this regard.[4]

The success rate of LAMS has been reported to be over 90% in pooled analyses[5,6] and a step-up approach with endoscopic transluminal drainage followed (if necessary) by endoscopic necrosectomy represents the best therapeutic approach for WON.[7–9]

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See Acknowledgements for other members of the i-EUS Group.
Received 14 February 2022; accepted 18 May 2022.

Although uncommon, adverse events (AEs) such as bleeding, infection, and buried stent syndrome have been reported after LAMS placement in up to 13% of cases.[9–11]

To this end, strong evidence on the predictive factors of AE occurrence is still lacking. An American prospective study found stent removal after 4 weeks and PFC size ≤7 cm as predictors of delayed AEs after LAMS placement.[11] However, due to the relatively rare incidence of AEs, the sample size (188 patients) was likely underpowered to accurately detect predictors of AEs. Additionally, several technical and clinical parameters were not tested including imaging of the PFC or etiology of underlying pancreatitis. Above all, simple logistic regression is not able to capture the real interactions among single predictive factors. A numeric predictive model able to quantify the risk for AE occurrence based on the interaction of several baseline parameters enables bedside application using single patient characteristics.[12]

In the current study we sought to build and validate a prognostic model based on a nomogram for prediction of AE occurrence in patients undergoing LAMS placement for PFC. Discrimination and calibration of the model were also explored.

METHODS

CLINICAL DATA WERE collated from gastroenterologists and endoscopists as part of a nationwide initiative from the Interventional Endoscopy and Ultrasound (i-EUS) group. These clinicians throughout the national territory of Italy were involved in performing endoscopic ultrasound (EUS)-guided drainage with LAMS. Approval for this retrospective study was ascertained by the Institutional Review Board of each participating institution or center in direct accordance with the Declaration of Helsinki. The protocol was registered on ClinicalTrials.gov (NCT03903523). The database collected 850 cases for the primary indications of gallbladder and biliary drainage. The current study protocol looked at patients who only had an EUS-guided drainage procedure for PFC using LAMS. Endoscopic procedures are described in Appendix S1.

Data collection

Using a centralized Web-based database, data were compiled and then extracted for analysis. Data extracted included patient demographics and extensive details regarding features of fluid collection (including type, measurement, site, cause of PFC, depth of extension, necrosis as estimated radiographically on magnetic resonance cholangiopancreatography [MRCP], extension, percentage of necrosis estimated by radiologists on MRCP, access site, appearance of main pancreatic duct [MPD] with computed tomography scan/magnetic resonance imaging) or EUS (i.e., intact, fully disconnection defined as abrupt discontinuation of MPD at the level of PFC, leak characterized as no discontinuation but having evidence of continuity with the PFC,[13] abnormal vessels such as portal vein thrombosis, peri-gastric varices, pseudoaneurysm). Additionally, we extracted data regarding LAMS placement (e.g., type and size, placement technique), as well as procedural data (corresponding to maneuvers during the procedure). Data following procedures were also extracted including resumption of enteral diet (grouped as under or over 48 h), length of hospital stay, follow-up procedures including further LAMS placement, percutaneous drainage, stent removal following PFC resolution, recurrence at follow-up, and AEs.

Outcomes

Using the ASGE lexicon,[14] AEs were defined, classified, and graded. We considered all symptomatic events related to LAMS placement including stent occlusion and migration, bleed, hemorrhage, infections (development of clinical signs of infection, such as fever and tachycardia combined with leukocytosis after the stent insertion), which led to extending the hospital length of stay, necessitated medical treatment, or additional procedural intervention.[14]

We defined stent dislodgement as the erroneous deployment of the LAMS during the procedure. This was usually a result of technical matters, including inadequate or undue retraction of the LAMS before the second flange was released. Concomitantly, stent migration occurred during the follow-up.

We defined technical success as the correct placement of LAMS. Clinical success was defined as the resolution of WON or PP (i.e., <2 cm on axial imaging 1–6 months after LAMS insertion) that did not require additional procedures. Centers were considered high competence after 10 procedures according to a recent consensus of experts.[15]

Statistical analysis

Demographic and patient data were expressed in terms of mean and standard deviation for continuous variables while categorical data were expressed using absolute frequencies. Using stepwise logistic regression, we initially analyzed baseline factors with a potential prognostic effect on AE

occurrence. Significant predictors in univariate analysis were entered in the multivariate model. Results were expressed in terms of odds ratio (OR) and 95% confidence interval (CI).

The multicenter nature of the study was considered by applying the K-means unsupervised machine-learning method where data were clustered according to the institution involved.[16]

Using the multivariate logistic regression model, a nomogram was built. The nomograph was internally validated using a bootstrap resampling method, where random samples were drawn with replacement from the original cohort. The model was repeatedly fitted using 1000 bootstrap samples and evaluated on its performance. This was done using the original sample.[17]

We used the Akaike information criterion (AIC) and Bayesian information criterion (BIC) to express the model's performance before and after bootstrapping validation. Methodological characteristics are outlined in Appendix S2.

Furthermore, discrimination of the model before and after bootstrapping-based validation was assessed using Nagelkerke's R^2 test as well as area under the receiver operating characteristic curve (AUC, or *c*-statistic).[18]

A calibration plot showed the correlation between the predicted mean AE probability versus the observed mean AE rate in deciles of patients with increasing values of the predicted probability. To allow more insight into calibration analysis, plots were drawn by a Loess smoother algorithm.[18] The Hosmer–Lemeshow test[19] was used to assess differences between predicted probability and observed AE rate. The calibration slope was assessed by logistic regression models and differences from their ideal values (0 and 1, respectively) using the Wald test.[18]

The main strength of this model is that, while in linear regression the information from different predictor variables is combined linearly, here the risk related to the range of possible combinations of predictors can be exactly predicted and quantified through a numeric score. Multiple linear regression analyses were also performed to establish an equation able to predict the AE occurrence risk.

Using two post-hoc settings, which included only cases of bleeding and buried stent syndrome (and excluded mild AEs unlikely to impact patient outcomes), the same model was tested and validated.

Homoskedasticity, collinearity, and normal distribution of residuals of the model were assessed and described in Appendix S3.

All statistical tests were two-tailed, and differences were considered significant at $P < 0.05$.

The statistical analysis was run using the rms and performance packages in R Statistical Software 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

OUR STUDY INVOLVED 516 patients with PFC who underwent LAMS placement across 30 secondary and tertiary care centers in Italy from January 2016 to July 2020. The baseline characteristics of the whole study population are reported in Table 1.

Outcomes

A detailed list of study outcomes is reported in Table 2. Overall, 76 AEs were observed (14.7%), of which bleeding (5.6%), infection (1.9%), stent migration (1.4%), and dislodgement (1.3%) were the most frequent. Moreover, five patients (0.9%) experienced buried stent syndrome, four patients stent occlusion (0.7%), and three cases of perforation (0.5%) were registered.

These events were managed conservatively in 17 cases (3.3%), with interventional radiology embolization in 11 patients (2.1%), or with endoscopy in 30 patients (6%). Surgery was needed in only two patients (0.4%). AEs were classified as mild in 24 patients (4.6%), moderate in 32 patients (6.2%), and severe in 13 patients (2.5%). Treatment-related death was registered in six cases (1.1%) and the overall mortality rate was 10.9%.

Predictive model

At univariate logistic regression, the appearance of MPD at preprocedural imaging/EUS (OR in the case of leak 2.51, 95% CI 1.06–5.97, $P = 0.03$; OR in the case of complete disruption 2.61, 1.53–4.45, $P = 0.01$), presence of abnormal vessels (OR in the case of perigastric varices 2.90, 1.31–6.42, $P = 0.008$; OR in the case of pseudoaneurysm 2.99, 1.75–11.93, $P = 0.002$), use of a multigate drainage technique (OR 3, 1.28–5.24, $P = 0.05$), and need of combined percutaneous drainage (OR 2.81, 1.03–7.65, $P = 0.04$) resulted as significant predictors of AE occurrence (Table 3). All of these variables were confirmed as significant predictors of AEs in multivariate analysis (Table 3).

For an individual estimate of the risk of AE occurrence based on the multivariate logistic regression model, a nomogram was constructed (Fig. 1). In particular, a score of 70 points was given in the case of pancreatic duct (PD) leak on EUS imaging and 80 points in the case of complete PD

Table 1 Baseline patients' characteristics

Variable	Total (n = 516)
Age (years)	61.64 ± 15.16
Sex	
Male	351 (68)
PFC type	
Pseudocyst	247 (47.9)
Walled-off necrosis	269 (52.1)
Percentage of necrosis	45.04 ± 20.56
Location	
Body	348 (67.4)
Head	87 (16.9)
Tail	81 (15.7)
Collection appearance	
Single	404 (78.3)
Multiloculated	112 (21.7)
Collection width (mm)	89.03 ± 61.9
Collection length (mm)	77.52 ± 45.68
Extension to paracolic gutter	
Not reported	15 (2.9)
No	367 (71.1)
Yes	134 (26)
EUS appearance of pancreatic duct	
Leak	36 (7)
No leak	324 (62.8)
Complete disruption	16 (3.1)
Unknown	140 (27.1)
Vessel appearance on EUS	
No alterations	415 (80.4)
Perigastric varices	34 (6.6)
Pseudoaneurysm	10 (1.9)
Portal vein thrombosis	21 (4.1%)
Splenic vein thrombosis	36 (7%)
Indication	
Abdominal pain	165 (32)
Early satiety	38 (7.4)
Infection	207 (40.1)
Outlet obstruction	60 (11.6)
Vessel thrombosis	8 (1.6)
Vomiting	20 (3.9)
Other	18 (3.5)
Etiology of pancreatitis	
Alcohol	92 (17.8)
Autoimmune	1 (0.2)
Biliary	254 (49.2%)
Idiopathic	68 (13.2%)
Post-ERCP	14 (2.7)
Post-operative	46 (8.9)
Trauma	18 (3.5)
Other	23 (4.5)
Type of stent	
Hot Axios	386 (74.8)
NAGI	90 (17.4)
Spaxus	7 (1.4)
Other	33 (6.4)
Access	
Needle + guidewire	150 (29.1)
Single stage	366 (70.9)
Fluoroscopic guide	
Yes	294 (57)
No	222 (43)
Stent diameter	
10 × 10	58 (11.2)
15 × 10	270 (52.3)
20 × 10	52 (10.1)
8 × 8	3 (0.6)
Other	133 (25.8)
Multigate drainage technique	
No	504 (97.7)
Yes	12 (2.3)
Second flange deployment	
Endoscopic view	175 (33.9%)
Intrachannel	341 (66.1)
Approach	
Transduodenal	38 (7.4)
Transgastric	466 (90.3)
Both	9 (1.7)
Other	2 (0.4)
Not reported	1 (0.2)
Stent dilation	
No	414 (80.2)
Yes	102 (19.8)
Necrosectomy	
No	307 (59.5)
Yes	208 (40.3)
Not reported	1 (0.2)
Necrosectomy in the same session	102 (19.8)
Endoscopic appearance of cavity	
Purulent fluid	224 (43.4)
Solid debris	169 (32.8)
Vessels	9 (1.7)
Other	103 (20%)
Not reported	11 (2.1)
Hydrogen peroxide irrigation	
No	362 (70.2)
Yes	143 (27.7)
Not reported	11 (2.1%)
Antibiotic irrigation	
No	486 (94.2)
Yes	19 (3.7)
Not reported	11 (2.1)
Nasocystic tube drainage	
No	432 (83.7)
Yes	73 (14.1)

Table 1 (*Continued*)

Variable	Total (n = 516)
Not reported	11 (2.1)
Pigtail use through stent	
No	450 (87.2)
Yes	66 (12.8)
Use of coaxial plastic stent within the LAMS	
No	13 (2.5%)
Yes	53 (10.2%)
Need of percutaneous drainage	
No	497 (96.3)
Yes	19 (3.7)
Days to stent removal	50.3 ± 64.92

Variables are reported as absolute numbers (percentage) or mean (standard deviation) when appropriate.
ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; LAMS, lumen-apposing metal stent; PFC, pancreatic fluid collection.

disruption; likewise, 75 points were assigned in the case of EUS evidence of perigastric varices and 95 points in the case of pseudoaneurysms, whereas the use of a multigate drainage technique corresponded to 85 points and the need for percutaneous drainage corresponded to 100 points (Fig. 1). An overall summary score beyond 200 points corresponded to a 50% probability of AE occurrence (Fig. 1).

Moreover, in order to predict the individual AE risk, a regression equation was also established by multiple logistic regression analysis based on regression coefficients:

$$[\text{Perigastric varices} \times 1.94] + [\text{Use of a multigate drainage technique} \times 1.79] + [\text{PD leak} \times 1.25] + [\text{PD distruction} \times 1.44] + [\text{Need of percutaneous drainage} \times 1.80] + 5.5$$

where the presence of the variable corresponded to 1, absence to 0.

The predictive model (including the same variables) was confirmed by excluding mild AEs and the nomogram is reported in Figure S1. In this case, given the lower rate of events, a summary point beyond 160 corresponded to a 40% risk of moderate up to fatal AEs.

Using the same variables and restricting the analysis to only cases of bleeding and buried stent syndrome, the predictive model was again confirmed (Fig. S2).

Table 2 Outcomes

	Total (n = 516)
Technical success	500 (96.9)
Clinical success	473 (91.7)
Adverse event rate	76 (14.7)
Type of adverse event	
Bleeding	29 (5.6)
Infection	10 (1.9)
Stent occlusion	4 (0.7)
Stent migration	8 (1.4)
Stent dislodgement	7 (1.3)
Perforation	3 (0.5)
Capnoperitoneum requiring drainage	1 (0.2)
Biliary stricture	1 (0.2)
Buried stent syndrome	5 (0.9)
Ab ingestis pneumonia	1 (0.2)
Acute cholecystitis	1 (0.2)
Death	1 (0.2)
Jaundice due to CBD compression	1 (0.2)
Outflow obstruction of the duodenal stent	1 (0.2)
Pneumoperitoneum with air in the portal vein	1 (0.2)
Septic shock	1 (0.2)
Severity adverse event	
Mild	24 (4.6)
Moderate	32 (6.2)
Severe	13 (2.5)
Fatal	6 (1.1)
Collection recurrence	35 (6.8)
Death	56 (10.9)
Management of adverse events	
Endo stent cleaning	6 (1.2)
Endoscopic hemostasis	8 (1.6)
Endoscopic stent removal	8 (1.6)
Endoscopic stent replacement	8 (1.6)
Additional stent insertion	2 (0.4)
Radiology percutaneous drainage	1 (0.2)
Interventional radiology embolization	11 (2.1)
Surgery	2 (0.4)
Conservative	17 (3.3)
Autoresolution with LAMS placement	1 (0.2)
Resolved after plastic biliary stent	1 (0.2)
Other	10 (1.9)

Data are shown as number (percentage).
CBD, common bile duct; LAMS, lumen-apposing metal stent.

Performance of the model and validation

Performance measures of the predictive model are reported in Table S1.

The model showed a c-index of 76.8% (95% CI 74–79%; Fig. 2). The AIC and BIC were 317.455 and 332.433, respectively, while R^2 Nagelkerke's test was 0.244 with a residual standard error of 0.135.

The model also showed proper calibration (Hosmer–Lemeshow $P = 0.23$) as shown by the calibration plot (Wald test for calibration slope $P = 0.64$; Fig. 3).

Table 3 Univariate/multivariate logistic regression analyses for prediction of adverse events

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Age	1.31 (0.90–1.90)	0.150		
Sex (reference female)	1.06 (0.78–2.3)	0.550		
Collection type (reference WON)	0.80 (0.49–1.31)	0.380		
Percentage of necrosis	0.99 (0.78–1.43)	0.890		
Location (reference body)	Head: 1.23 (0.65–2.3)	0.510		
	Tail: 0.74 (0.35–1.57)	0.440		
Collection width (<70 mm)	1.16 (0.71–1.92)	0.530		
Collection length (<70 mm)	0.86 (0.55–1.73)	0.250		
Collection appearance (reference single)	1.14 (0.64–2.03)	0.650		
Extension to paracolic gutter (reference no)	1.01 (0.58–1.77)	0.920		
PD appearance on imaging (reference no leak)	Leak: 2.51 (1.06–5.97)	**0.030**	Leak: 2.29 (1.04–5.5)	**0.050**
	Complete disruption: 2.61 (1.53–4.45)	**0.010**	Complete disruption: 1.44 (1.14–5.61)	**0.030**
	Unknown: 1.08 (0.67–2.31)	0.340		
Vessel appearance on imaging (reference no alterations)	Perigastric varices: 2.90 (1.31–6.42)	**0.008**	Perigastric varices: 2.15 (1.11–3.75)	**0.040**
	Pseudoaneurysm: 2.99 (1.75–11.93)	**0.002**	Pseudoaneurysm: 2.41 (1.45–6.22)	**0.002**
	Portal vein thrombosis: 1.64 (0.53–5.07)	0.380		
	Splenic vein thrombosis: 1.68 (0.70–4.04)	0.240		
Indication (reference infection)	Abdominal pain: 0.97 (0.52–1.79)	0.34		
	Early satiety: 1.50 (0.60–3.75)	0.360		
	Other: 1.90 (0.58–6.21)	0.270		
	Outlet obstruction: 1.84 (0.88–3.84)	0.100		
	Vessels thrombosis: 2.22 (0.42–11.54)	0.330		
	Vomiting: 0.74 (0.16–3.72)	0.720		
Etiology of pancreatitis (reference biliary)	1.94 (0.78–2.22)	0.140		
Type of stent (reference Hot Axios)	NAGI: 1.17 (0.63–2.19)	0.600		
	Spaxus: 0.84 (0.55–2.1)	0.760		
	Other: 0.50 (0.19–1.04)	0.910		
Access (reference single stage)	1.15 (0.67–1.94)	0.600		
Use of fluoroscopy (reference yes)	0.89 (0.54–1.47)	0.670		
Stent diameter (reference 15 × 10)	10 × 10: 1.07 (0.47–2.45)	0.860		
	20 × 10: 1.59 (0.73–3.74)	0.440		
	8 × 8: 3.35 (0.29–11.1)	0.370		
	Other: 1.33 (0.74–2.37)	0.630		
Multigate drainage technique (reference no)	3 (1.28–5.24)	**0.050**	2.33 (1.15–8.39)	**0.020**
Second flange release (reference intrachannel)	1.08 (0.65–1.80)	0.74		
Approach (reference transgastric)	0.70 (0.24–2.03)	0.23		
Stent dilation (reference no)	1.55 (0.88–2.74)	0.120		
Necrosectomy (reference no)	1.58 (0.97–2.58)	0.060		

Table 3 (*Continued*)

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Endoscopic appearance of cavity (reference purulent fluid)	Solid debris: 1.57 (0.89–2.76)	0.400		
	Vessels: 3.64 (0.86–5.15)	0.130		
	Other: 1.19 (0.61–2.31)	0.600		
Hydrogen peroxide irrigation (reference no)	0.71 (0.40–1.27)	0.260		
Antibiotic irrigation (reference no)	1.12 (0.45–2.13)	0.4		
Nasocystic drainage (reference no)	0.67 (0.31–1.47)	0.32		
Pigtail use through the stent (reference no)	0.90 (0.42–1.90)	0.780		
Use of coaxial plastic stent within the LAMS (reference no)	0.89 (0.55–1.53)	0.39		
Need of percutaneous drainage (reference no)	2.81 (1.03–7.65)	**0.040**	2.82 (1.44–8)	**0.009**
Days to removal (reference <30)	1.32 (0.78–3.21)	0.190		
Experience of the center (reference high)	1.40 (0.75–2.12)	0.290		

Significant values are reported in bold.
CI, confidence interval; PD, pancreatic duct; WON, walled-off necrosis.

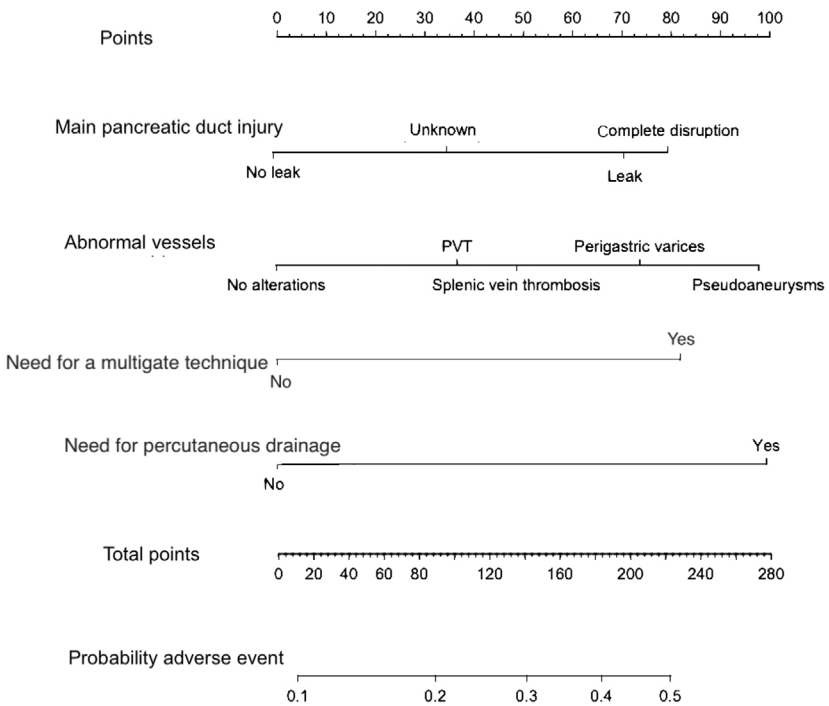

Figure 1 Nomogram predicting the probability of experiencing an adverse event. Main pancreatic duct injury, vessels abnormalities, use of a multigate drainage technique, and the need for percutaneous drainage resulted significant predictors of adverse events. An overall summary score beyond 200 points corresponded to a 50% probability of adverse event occurrence. PVT, portal vein thrombosis.

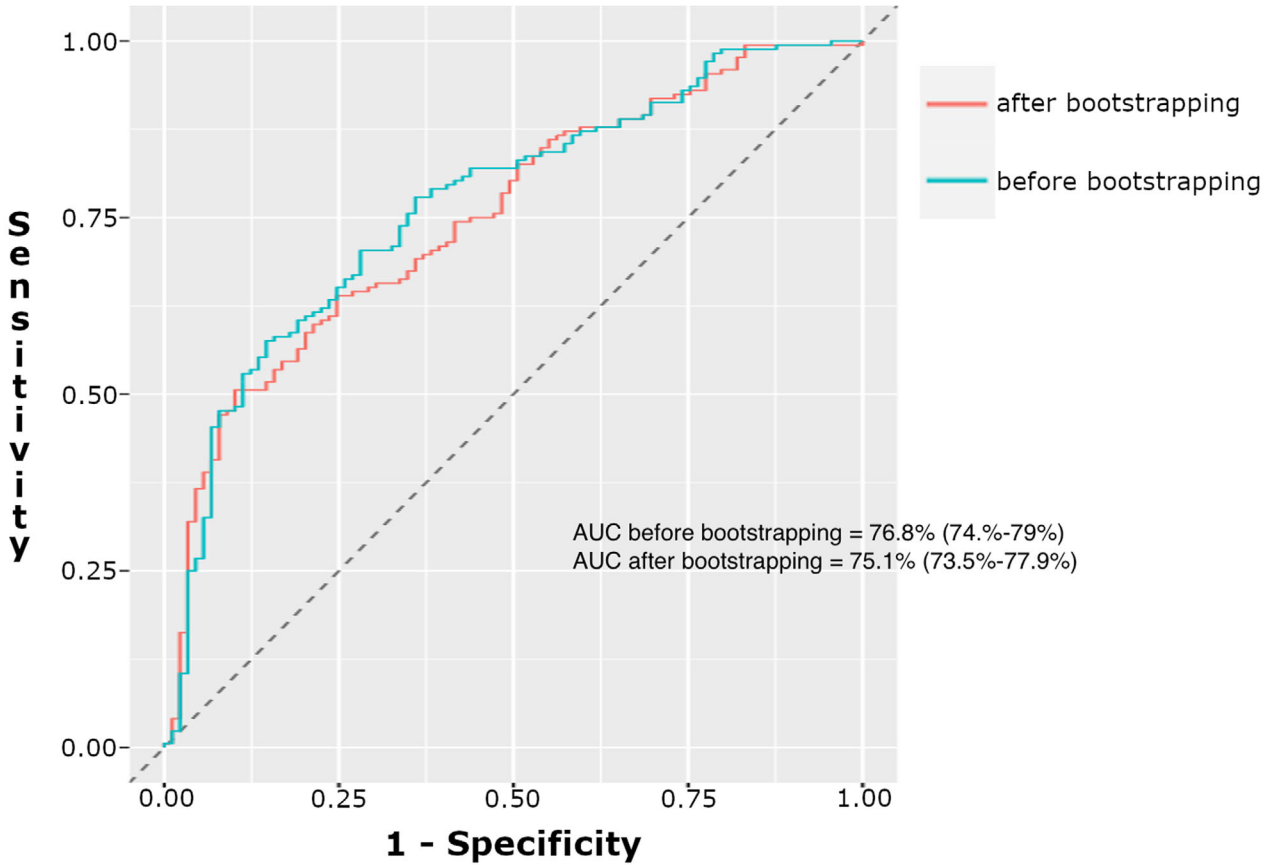

Figure 2 Receiver operating characteristic curve and the corresponding area of the predictive model. Blue line corresponds to the analysis before internal validation and red line corresponds to the analysis after bootstrapping-based internal validation.

No evidence of heteroskedasticity, collinearity, or non-normal distribution of residuals were detected in the predictive model (Fig. S3).

The performance of the model result was optimal even when excluding mild AEs, as reported in Table S1 and in Figure S4. In fact, the AUC and AIC were 74.8% (72–78%) and 319.523 when the model was restricted to more severe AEs.

The internal validation of the model based on a bootstrap method (1000 repetitions), showed an AUC value of 75.1% (95% CI 73.5–77.9%) (Table S1 and Fig. 2). When the multivariate regression model was adjusted excluding mild AEs, the corresponding AUC after bootstrap validation was not significantly different (73.6%, 71.8–77.3%; Table S1 and Fig. S4).

DISCUSSION

TO THE BEST of our knowledge, our study represents the first attempt to build a prognostic score model for AE occurrence in patients with PFC treated with LAMS.

Injury of MPD, abnormal vessels close to the PFC, use of a multigate drainage technique, and the need for percutaneous drainage were significant predictors of AE occurrence both in univariate and multivariate logistic regression analysis.

The relationship between MPD and PFC outcome has been recently suggested in a study which demonstrated an increased PFC recurrence and higher morbidity in patients with complete PD disruption.[20] Our study found that both complete disruption and even PD leak can be considered significant predictors of AEs in this setting, thus pointing out the importance to ascertain the integrity of the MPD in patients undergoing EUS-guided drainage. Indeed, besides being an expression of the severity of injury, MPD damage leads to continuous pouring of pancreatic juice into the collection, thereby increasing the risk of vessel erosion and/or recurrence after early LAMS removal.

The use of a multigate drainage technique can be related to the complexity of the procedure. On the other hand, the

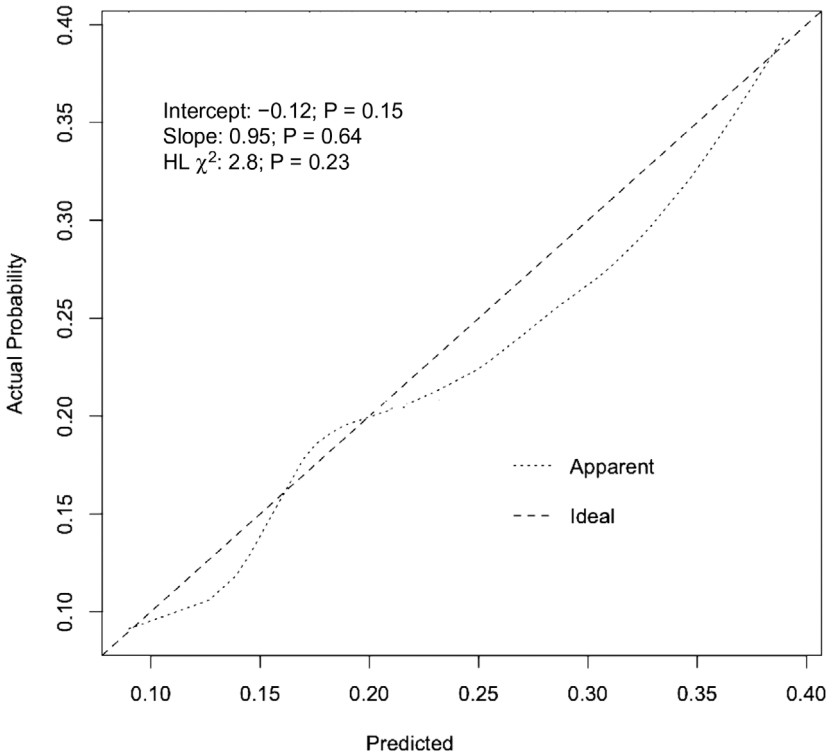

Figure 3 Calibration plot. Smoothed (Loess) calibration plots reporting increasing predicted probability of adverse events by the assessed model. The diagonal line indicates the ideal line of perfect correspondence of predicted to observed adverse event rate. *P*-values for intercept and slope are from Wald test. HL, Hosmer–Lemeshow test.

need for percutaneous drainage may underscore the severity of pancreatic damage and the extent and complexity of the collection.

PFC size and timing of LAMS removal were not confirmed as significant predictors of AEs, unlike the previous study by Bang *et al.*[11] Possible explanations of these results are probably multiple and composite. Bang *et al.* postulated that PFCs smaller than 7 cm could drain more rapidly, thus requiring LAMS removal within 3–4 weeks to avoid vessel erosions. However, besides the size of the PFC, other factors such as the shape, content, and the location could be related to rapid emptying of the collection. More importantly, Bang *et al.* did not evaluate other important factors potentially associated with AEs, such as vascular abnormalities. The alarming data that arose from Bang *et al.*'s study greatly worried the community of endoscopists dedicated to this kind of procedure. After the publication of the article, the EUS-interventional community changed the way of treating PFC with LAMS by introducing the definite timing of 3 weeks for LAMS removal. We hypothesized that our results, in contrast with the above-mentioned study, could help redefine this value and its clinical relevance. However, we believe that LAMS management can be tailored for each patient. Indeed, it seems reasonable to perform a cross-sectional imaging after 3–4 weeks to assess PFC resolution and, more importantly, the position of the LAMS distal flange. If the PFC is completely drained, the LAMS can be removed. Differently, if the PFCs is still present, the LAMS can be safely left in place if the distal flange is not close to major vessels. Finally, in the case of persistent PFCs and the risk of major vessel erosion by the distal flange of the LAMS, the metallic stent could be changed with DPPS. Clearly, we think these results are not conclusive and a powered randomized trial is needed to confirm them.

It could be argued that the identified predictors of AE cannot be modified, and that therefore the nomogram has no clinical relevance. Conversely, we think it does, as identifying patients at greater risk of AE could drive different therapeutic strategies. For example, not having confirmed the removal time of LAMS as predictors of AE could allow a tailored management protocol different from the standard, when needed.

The AE rate observed in our series is slightly higher than the incidence of complications reported in prior studies (14% vs. up to 10%).[21–24] However, it should be noted that about

one-third of these events were mild, and thus unlikely to impact patient outcomes. The long follow-up in addition to close observation in our study may have also contributed to a higher chance for reporting long-term complications missed in previous studies. Furthermore, the large number of centers involved might have led to a "real-life" representation of the use of LAMS in patients with PFC, and hence, not restricted to high-volume centers. All the data in the literature comes from referral centers, where the high expertise of the operators could justify lower AE rates.[25–27] Of note, the rate of AEs was not affected by the type of PFC (whether WON or PP), as noted in prior reports.[11,23,28]

There are some weaknesses to our study. First, the retrospective nature of the report may have introduced some selection and outcome biases. However, the definition of the outcome and the completeness of the data collection were homogeneous throughout the centers involved in the study. Second, the lack of external validation might represent a further limitation to the analysis. Nevertheless, the model building process and its performance were simultaneously validated in a broad range of random samples, thus obviating an external cohort, as recently confirmed in simulation studies.[17,29]

In conclusion, patients with preprocedural evidence of MPD leak/disruption or vessels alterations on preprocedural imaging/EUS, needing combined endoscopic/percutaneous drainage and/or a multigate drainage technique, are at higher risk of AE occurrence. These subjects may require a more careful indication and approach for LAMS placement as well as stricter follow-up.

ACKNOWLEDGMENTS

OTHER MEMBERS OF the i-EUS Group: Daryl Ramai[11], Edoardo Forti[12], Maria Chiara Petrone[13], Roberto Di Mitri[14], Debora Berretti[15], Germana De Nucci[16], Raffaele Macchiarelli[17], Mauro Lovera[18], Fabia Attili[19], Mario Luciano Brancaccio[20], Alessandro Redaelli[21], Enrico Tasini[22], Marco Ballarè[23], Franco Coppola[24], Nicola Leone[25], Luigi Cugia[26], Roberto Grassia[27], Monica Sbrancia[28], Thomas Togliani[29], Pietro Fusaroli[30], Claudio De Angelis[31], Fabio Cipolletta[32], Mauro Manno[33], Roberta Badas[34], Valeria Pollino[35], Lorenzo Camellini[36], Laura Bernardoni[2], Elisabetta Conte[13], Andrea Lisotti[30], Massimiliano Mutignani[12], Paolo Giorgio Arcidiacono[13].

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CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

FUNDING INFORMATION

NONE.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Appendix S1 Procedures.

Appendix S2 Parameters used to assess model performance.

Appendix S3 Model diagnostics.

Figure S1 Nomogram for prediction of adverse events excluding mild adverse events.

Figure S2 Nomogram for prediction of adverse events considering only bleeding and buried stent syndrome.

Figure S3 Check of the assumptions of the model.

Figure S4 Performance of the model before and after bootstrapping-based internal validation excluding mild adverse events.

Table S1 Performance of the model in the training cohort and after boostrapping-based internal validation assessed for overall adverse events and excluding mild adverse events.