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External Validation of The Paddington International Virtual Electronic Chromoendoscopy Score As A Good Endoscopic Score to Define Mucosal Healing and Predict Long-term Clinical Outcomes in Ulcerative Colitis

Running title：PICaSSO in Ulcerative Colitis

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Ge Chong RUAN and Xin JIN, sharing the first authorship, contributed to collection of data, statistical analysis and manuscript writing and editing.

Wei Xun ZHOU and Yan YOU contributed to the histological scores and manuscript editing.

Marietta IACUCCI, Subrata GHOSH and Xian Yong GUI contributed to the design of the study, manuscript editing and intellectual review.

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Abstract

Aims: To define endoscopic and histological remission in ulcerative colitis accurately, several score systems have been established. A novel Paddington International Virtual ChromoendoScopy ScOre (PICaSSO) virtual electronic chromoendoscopy (VEC) was recently developed, validated, and reproduced to assess inflammation grade and predict prognosis. We externally verified and validated the clinical value of the PICaSSO score in UC patients.

Methods: This prospective study enrolled 63 UC patients. The Mayo Endoscopic Score (MES), UC Endoscopic Index of Severity (UCEIS), and PICaSSO score were adopted for endoscopic evaluation. All biopsies were scored using the Robarts Histological Index (RHI), Nancy Histological Index (NHI), and Extent, Chronicity, Activity, and additional findings (ECAP). Patients with an endoscopic MES of 0-1 at baseline were followed up with the median time of 23.5 months.

Results: PICaSSO was strongly correlated with other endoscopic and histological scores. PICaSSO ≤3 had advantages in assessing histological remission (HR), with the highest accuracy of 88.9% for ECAP-HR. Relapse-free survival rates were significantly different between patients with MES 0 and MES 1 and patients with PICaSSO ≤3 vs＞3 (P = 0.010 and 0.018, respectively).

Conclusions: PICaSSO was externally validated with strong correlations with other endoscopic and histopathologic scoring systems in UC, and PICaSSO-ER might potentially predict the better long-term clinical outcomes in UC patients.

Keywords: Clinical Outcomes; Endoscopic Remission; Histological Remission; Ulcerative Colitis; Virtual Electronic Chromoendoscopy

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Introduction

Ulcerative colitis (UC) is an inflammatory immunologic disorder involving the colon and rectum characterized by relapsing superficial mucosal inflammation.[1] The diagnosis of UC is based on clinical symptoms, endoscopic evaluation and histological analysis.[2] Many scoring systems in UC are currently available for the evaluation of disease activity, including the Truelove-Witts severity score,[3] Mayo Clinic Score,[4] and UC Endoscopic Index of Severity (UCEIS).[5] With the evolution of the treatment target from clinical remission to mucosal healing (MH), the assessment of endoscopic remission or histological remission (ER and HR) has received much more attention. Endoscopic findings are included in the Mayo score and defined as the Mayo Endoscopic Subscore (MES),[6] which is primarily based on findings under white light. MES 0-1 is defined mainly as ER; however, many studies have indicated a totally different prognosis between patients with MES 0 and MES 1, and even in patients with MES 0.[7,8] On account of this point, the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease)-II has defined complete endoscopic healing as MES = 0, or UCEIS ≤1, associated with better outcomes.[9]

However, endoscopy do not necessarily distinguish mild and quiescent diseases, and there is a growing support for histological assessment for microscopic activity.[7] A recent study on endpoints of ustekinumab, showed that endoscopic improvement defined by MES in combination with HR outperformed in predicting inflammatory activity than endoscopic or histological assessment individually.[8] Whether double

remission (DR), combined endo-histological remission, exactly have additional impact on outcomes has not been validated.

Meanwhile, as precision medicine develops, modern imaging-advanced instruments have greatly improved the detection of subtle mucosal details and have been recommended for assessment by the latest European Society of Gastrointestinal Endoscopy Guideline.[10, 11, 12, 13] With advanced techniques, ER is getting closer to HR.[14] Experts have gradually recommended virtual electronic chromoendoscopy (VEC) as a better alternative, reducing the gap between endoscopic and histological assessment.[15] Recently, a novel VEC score, the Paddington International virtual chromoendoScopy ScOre (PICaSSO), was developed, combining the mucosal architecture under white light and vascular architecture under VEC.[16] It was strongly correlated with the MES and UCEIS and many histological indices, such as the Nancy Histological Index (NHI),[17] Robarts Histological Index (RHI),[18] Geboes score,[19] and Extent, Chronicity, Activity, Plus additional findings (ECAP).[20] It had a good interobserver agreement and PICaSSO ≤3 had accurate predictive potential for 6-month and 12-month remission in an international multicenter study.[21] Furthermore, it proved good reproducibility and could be applied to all VEC platforms.[22]

This prospective observational study aimed to investigate the correlation between the PICaSSO score and other endoscopic or histological scores and compare their diagnostic performance to predict ER and HR in a new cohort of patients. Furthermore, we evaluated relapse-free survival in patients with an MES of 0-1 at baseline and

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explored the predictive value of PICaSSO-ER and other ERs/HRs. And we investigated the performance of DR in predicting outcomes, compared with non-DR (NDR).

Accepted Article

Methods

Patient Cohort and Enrollment

A prospective open cohort study was performed at Peking Union Medical College Hospital. All eligible adult patients met the inclusion criteria: 1) diagnosed as UC according to the consensus;[23] 2) accepted colonoscopy procedures between June 2018 and October 2019; 3) offered informed consent to participate in the study and agreed to be followed up. Exclusion criteria included inability to provide consent or refusal of follow-up, pregnancy or breastfeeding, Boston bowel preparation score ≥4 during colonoscopy, failure of cecal intubation, contraindication or intolerance of colonoscopy. Patients were also excluded if they had Crohn's disease, unclassified IBD, ischemic colitis, infectious colitis, etc. The flowchart of the study is shown in Figure 1.

Study Variables at Baseline

Data at the time of index colonoscopy were collected, including demographics, Montreal classification, laboratory tests, endoscopic assessments, histopathologic features, and medications.

Accepted Article

Clinical disease activity status was categorized as remission or mild, moderate, or severe disease activity based on the Mayo total score (0-2 remission, 3-5 mild, 6-10 moderate, 11-12 severe)[4]. Disease extent was defined according to the Montreal Classification and categorised as proctitis (E1), left-sided colitis (E2), and extensive colitis (E3)[16].

Endoscopic assessment

All colonoscopies were performed by one expert gastroenterologist (JL), who was well trained and familiar with VEC. All patients underwent polyethylene glycol-based bowel preparation prior to their colonoscopy. Colonoscopies (EC-3890Fi and EC38-i10F) were assessed using an HD Pentax (Tokyo, Japan) EPK-i7000 before and after Oct 2018, and three modes: iScan1, iScan2 and iScan3, were simply switched in real-time with the button of the handpiece of the endoscope, whose standardized settings were reported recently[21].

During withdrawal, the endoscopist collected targeted images and took at least two biopsies from the most inflamed lesions macroscopically or the representative sites at the rectum or sigmoid if there were no inflamed lesions macroscopically. After the colonoscopy, the endoscopist evaluated the images captured for the MES and UCEIS scores under white light and then for the PICaSSO score with VEC (Figure 2). For individual endoscopic severity scores, results were recorded in the form of each item, and then summed up by computer calculation systems, blinded to estimators. Details of

the MES, UCEIS and PICaSSO scores are shown in Supplemental Tables 1-3. The definition of ER was MES 0-1, UCEIS ≤1, or PICASSO ≤3.[5,6,21,24]

Accepted Article

Histological assessment

Biopsies were prepared in formalin and then processed via routine protocols into hematoxylin-eosin-stained glass slides. Each slide was scored using the NHI, RHI, and ECAP，recording concrete items also, by one expert gastrointestinal pathologist (WXZ) who was blinded to the endoscopic scores. For NHI, three key histological components were assessed, including acute inflammatory cell infiltration, chronic inflammatory cell infiltration and ulceration. Next, RHI focused on four histological markers consisting of the presence of neutrophils in the lamina propria or epithelium, chronic inflammatory cell infiltrate, and erosions or ulceration. ECAP contains comprehensive items: 1) extent of mucosal inflammation; 2) chronicity; 3) activity; and 4) plus other additional findings (e.g. eosinophilia and lymphoid follicles). The definition of HR was RHI ≤3 (with absence of neutrophils), NHI ≤1 or ECAP ≤4.[5,17,18,20,25]

Long-term follow-up

All the patients with an MES of 0-1 at baseline accepted regular face-to-face or telephone interviews. UC relapse was defined as an increased number of bowel

movement and/or the occurrence of blood in stool, which caused clinical specified outcomes. Clinical specified outcomes included UC relapse-related hospitalisation or colectomy, and initiation or enhancement in medical therapy, including corticosteroids, immunomodulators and biologics.

Primary and secondary outcomes

The primary outcome was to systemically evaluate the correlation between several endoscopic and histological scores.

The secondary outcomes were as follows:

(1) To evaluate the potential predictive prognosis of each ER or HR for clinical relapse.

(2) To compare the diagnostic performance of three endoscopic scores to predict HR.

Statistical analysis

The mean ± standard deviation (SD) was estimated for normally distributed continuous variables, and *Student's t-test* was used to analyze the significant differences between the two groups. Continuous nonnormally distributed data were expressed as the median (interquartile range), and a nonparametric test was used for two-group comparisons. Categorical data were reported as counts and proportions, and the difference was assessed by *Fisher's* exact test.

Accepted Article

Pearson's test was conducted to clarify the correlation between the three histological scores. Correlations among the three endoscopic scores and histological scores were investigated using Spearman's correlation coefficients. A very strong correlation was defined as 0.80 to 1.0, a strong correlation as 0.60 to 0.79, a moderate correlation as 0.40 to 0.59, and a weak correlation as 0.20 to 0.39. The agreement between certain ERs and HRs was calculated as the kappa coefficient.

Kaplan–Meier survival curves for patients with survival free of clinical relapse were developed, and the log-rank test was used to assess significance. A *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM GraphPad Prism 9.

Ethical considerations

This study was approved by the Ethics Committee of PUMCH (No. ZS-1748). Patients enrolled in the study all gave written informed consent. The anonymity of all patients was safely protected.

Results

Baseline Demographics and Clinical Characteristics of UC Patients

A total of 63 UC patients were finally enrolled in the study, and their baseline characteristics were shown in Table 1. The mean age was 40.9±13.8 years, and 50.8%

Accepted Article

were male. The prevalence of the disease extent was 17.5% for E1, 22.2% for E2, and 60.3% for E3. The disease statuses of 27 (42.9%), 21 (33.3%) and 15 (23.8%) patients were remission, mild and moderate active disease, respectively.

Correlations among different endoscopic scores and histological scores

Significant correlations among the three endoscopic scores were found. PICaSSO showed a very strong correlation with MES score (r = 0.916, *P* <0.01) and UCEIS score (r = 0.904, *P* <0.01). The UCEIS correlated very strongly with the MES (r = 0.887, *P* <0.01).

Meanwhile, these very strong correlations can also be seen among ECAP, RHI and NHI, with Pearson coefficients ranging from 0.843 to 0.876.

Spearman correlation coefficients between endoscopic scores and histological scores are presented in Table 2. A strong correlation between PICaSSO and ECAP (r = 0.781, *P* <0.01), RHI (r = 0.658, *P* <0.01), and NHI (r = 0.661, *P* <0.01) was notable. MES with ECAP was the only group that correlated very strongly (r = 0.808, *P* <0.01), and MES was strongly correlated with RHI (r = 0.720, *P* <0.01) and NHI (r = 0.723, *P* <0.01). The UCEIS also displayed a strong correlation with histological scores. For histological scores, ECAP seemed to present better correlations with all endoscopic scores.

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Accuracy of Endoscopic scores in Histological-Remission prediction

The diagnostic performances of ER to HR are shown with sensitivity, specificity, and accuracy in Table 3. Generally, PICaSSO-ER performed better in assessing ECAP-HR and NHI-HR than RHI-HR. PICaSSO-ER was highly likely to reflect HR, with the highest accuracy of 88.9% for ECAP-HR, 85.7% for NHI-HR, and 81.0% for RHI-HR. The UCEIS-ER assessing HR showed an accuracy of 84.1% for ECAP-HR, 84.1% for NHI-HR, and 82.5% for RHI-HR. MES-ER had lower accuracy in predicting HR than UCEIS-ER and PICaSSO-ER, especially for ECAP-HR, with the lowest accuracy of 71.4%.

The predictive potential of each ER or HR for the long-term prognosis of UC patients with MES 0-1 at baseline

Twenty-six UC patients with an MES of 0-1 completed the median of 23.5 (16.25, 27.75) months of follow-up. At baseline, 7 of 26 (26.9%) were on topical therapies, 19 (73.1%) were treated with ASA, 4 (15.4%) with TCM, 1 (3.8%) with corticosteroids, 1 (3.8%) with biologics and 2 (7.7%) with immunomodulators. Nine (34.6%) patients displayed specified outcomes in therapy. The median time of specified outcomes were 17 (10, 19) months, calculated including only patients who experienced a relapse during the study period. The shortest relapse duration was 4 months in a patient on suppository ASA therapy.

Figure 3 presents the Kaplan–Meier curves for relapse-free survival of UC patients with ER versus non-ER and HR versus non-HR. The results of the log-rank test showed significantly increased survival rates in the MES = 0 versus MES = 1 (HR = 0.113; 95% CI, 0.030-0.417; $P = 0.010$) and PICaSSO ≤3 versus PICaSSO >3 (HR = 0.189; 95% CI, 0.050-0.718; $P = 0.018$) groups. However, for patients with UCEIS≤1, the specified clinical outcome events were not significantly different from UCEIS >1 ($P = 0.104$). Analysis showed that the differences in HR defined by histology scores were not significant (RHI ≤3 vs RHI >3, $P = 0.730$; NHI ≤1 vs NHI >1, $P = 0.406$), except for ECAP, which had a slightly larger difference (ECAP ≤4 vs ECAP >4, $P = 0.067$). A further analysis showed that MES 0 combined with ECAP ≤4 was significantly different in predicting outcomes compared with NDR (Log Rank $P = 0.030$). There was no significant difference of PICaSSO-ER combined with ECAP-HR, RHI-HR or NHI-HR compared with NDR ($P = 0.067$, 0.130 and 0.237, respectively).

Discussion

As a novel endoscopic score, PICaSSO has been developed and validated as a potential endoscopic score because of its predictive value of ER and HR and high interobserver agreement[21]. In account of the strict inclusion criteria and only 1-year follow-up in the previous multi-center study, it still needs external validation in routine clinical practice. In this prospective study, we revealed the strong correlation among the

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endoscopic scores (PICaSSO, MES, and UCEIS), as well as histological scores (ECAP, RHI and NHI). We found the accuracy of PICsSSO-ER for the prediction of HR was comparable with widely-used MES-ER and UCEIS-ER, and showed the favorable value in predicting ECAR-HR. Finally, PICaSSO-ER individually could predict better relapse-free survival during the median 2-year follow-up in UC patients with MES 0-1 at baseline.

Unlike Crohn's disease, most studies confirmed the strong correlation between endoscopic and histological scores in UC patients.[26] However, the cutoff values of MES-ER and UCEIS-ER have not yet been confirmed, and there is an absence of a validated definition of MH.[27,28,29] In general, ER contains the absence of friability, blood, erosions and ulcers in all visualized segments in the colorectal mucosa.[30,31] Routine endoscopies can evaluate the majority of UCs at the active phase, but do not necessarily reflect quiescent microscopic disease, especially when MES 0-1 are considered together as the endpoint.[32] The interobserver agreement rates of endoscopic diagnosis are not stable. In Kanazawa's study, the parameter "absent vascular pattern" in MES displayed low interobserver reliability among IBD experts and nonexperts.[33] Meanwhile for better detection of residual inflammation, histological assessment might indicate complete resolution better.[26] Using VEC, vascular pattern is not absent but visible with abnormalities as defined in PICaSSO score. Our study, designed as a single operator based on commonly used criteria, showed PICaSSO-ER had the best

diagnostic performances of ECAP-ER. In another similar study, the PICaSSO score also showed superior performance in assessing NHI-HR and RHI-HR.[21]

Before the announcement of STRIDE-II, MES 0-1 is identified as mucosal remission in routine clinical practice.[34] However, it has been indicated that MES ≤1 might not be an ideal indicator recently. Our results also showed a significant difference in relapse-free survival between patients with MES 0 and MES 1, consistent with several other studies.[35,36] Meanwhile, it is noteworthy that our study suggested that PICaSSO ≤3 individually or combined with ECAP ≤4 was more likely to predict preferable outcomes, which has shown the promising potential as the endpoint or target of medication.

It is still undetermined whether ER combined with HR could have more advantages to predict the long-term outcomes. Christensen. et al. proposed "histological normalization", which could better predict good outcomes than histological quiescence and ER alone.[37] A prior meta-analysis also indicated the incremental benefit of achieving double remission based on long-term duration of follow-up in UC patients with MES 0.[38] More specifically, we found that MES 0 combined with ECAP-HR was associated with a substantially better prognosis than non-double remission UC. In account of the very limited number of MES 0, whether this more rigorous endpoint, double remission, is supposed to replace clinical routine target, it still needs more multi-center comparative studies involving multiple combos of ER and HR in future. However, the difference of PICaSSO-ER combined with HR didn't reach statistical

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significance, which was consistent with the previous multi-center study.[39] Perhaps it strongly suggested that PICaSSO-ER was sufficient to distinguish different prognosis of mild or quiescent UC patients(MES 0/1), while MES alone had limited capability.

The highlights of this study are as follows: first, we used the VEC and incorporated the recently validated PICaSSO into the design. VECs are now available on most endoscopies in the clinic and display much subtler images than conventional white light.[40] Second, in contrast to the previously published multicenter study, the inclusion criteria of this study are not strict and appropriate for real-world clinical practice. Biopsies were taken and evaluated in the most inflamed lesions macroscopically, which are also efficiently conducted. Finally, this study had a median 2-year long-term follow-up, the longest for PICaSSO, which could be useful to determine changes in outcomes along the natural course of the disease.

This study had some relevant limitations. First, in the case of the single-centre study, the number of participants was limited, especially for UC patients with an MES of 0-1, probably due to the COVID-19 pandemic and the desire for unnecessary colonoscopy in patients with MES-ER. Meanwhile, for the long-term follow-up, the telephone interview, an pivotal approach to collect information from the patients in account of normalization of the epidemic. However, it was still a powerful research, because our team were composed of IBD specialists, which enabled to guarantee the quality of enrollment and crucial endoscopic and histological assessment. Second, the exact threshold of recently developed scores in our study needs further examination，

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especially when the endoscopic score and histological score were all recorded by one endoscopist and one pathologist individually. Fortunately, it is noteworthy that a brief training module has been established and non-expert endoscopists and a trainee can present the same performance as an experienced endoscopist after a short learning for the PICaSSO score.[22] Third, as various medications were prescribed by former physicians, may alter the distribution and nature of mucosal changes, further comprehensive multivariate analyses are needed, such as therapy strategies, dosage regimens and administrations. Finally, many new scores have continued to emerge: Toronto IBD Global Endoscopic Reporting score,[41] PICaSSO Histologic Remission Index,[42] Capsule Scoring of Ulcerative Colitis,[43] and The Mucosal Analysis of Inflammatory Gravity by i-scan TE-c Image.[44] These scores are not involved and compared with PICaSSO in this study, which comparative studies will be conducted in future.

In conclusion, PICaSSO was externally validated with strong correlations with other endoscopic and histopathologic scoring systems in UC, and PICaSSO-ER might potentially predict the better long-term clinical outcomes in UC patients, which added more evidence about the predict value of PICaSSO-ER.

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Accepted Article

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Tables

Table 1. Baseline demographics and clinical characteristics of Patients

Characteristics	Patients (n=63)
Gender Male n (%)	32 (50.8%)
Age at enrollment, y (mean ± SD)	40.9 ± 13.8
Disease extension	
E1	11 (17.5%)
E2	14 (22.2%)
E3	38 (60.3%)
Clinical disease activity based on Mayo total score	
Remission	27 (42.9%)
Mild	21 (33.3%)
Moderate	15 (23.8%)
Endoscopic activity	
Mayo Endoscopic Subscore n (%)	
MES = 0	13 (20.6%)
MES = 1	13 (20.6%)
MES = 2 or 3	37 (58.7%)

UCEIS n (%)	
Remission (<1)	18 (28.6%)
Active (>1)	45 (71.4%)
PICASSO n (%)	
Remission (≤3)	15 (23.8%)
Active (>3)	48 (76.2%)
Histological activity	
ECAP n (%)	
Remission (≤4)	8 (12.7%)
Active (>4)	55 (87.3%)
RHI n (%)	
Remission (≤3)	15 (23.8%)
Active (>4)	48 (76.2%)
NHI n (%)	
Remission (≤1)	16 (25.4%)
Active (>1)	47 (74.6%)
Therapy at baseline	
No treatment	1 (1.6%)

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ASA †	49 (77.8%)
Corticosteroids	5 (7.9%)
Immunomodulators	5 (7.9%)
Biologics	2 (3.1%)
TCM	6 (9.5%)

Abbreviations: MES, Mayo Endoscopic Subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PICaSSO, Paddington International Virtual ChromoendoScopy ScOre; ECAP, 'Extension, Chronicity, Activity, Plus additional findings'; RHI, Robarts Histological Index; NHI, Nancy Histological Index. ASA, aminosalicylic acid; TCM, traditional Chinese medicine.

†Among patients who were treated with ASA, 43 received oral ASA,12 suppository, 4 enema.

Table 2. The Correlation Between Endoscopic Indices and Histological Indices ‡

	ECAP	RHI	NHI
MES	0.808**	0.720**	0.723**
UCEIS	0.775**	0.699**	0.694**
PICaSSO	0.781**	0.658**	0.661**

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Abbreviations: MES, Mayo Endoscopic Subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PICaSSO, Paddington International Virtual ChromoendoScopy ScOre; ECAP, 'Extension, Chronicity, Activity, Plus additional findings'; RHI, Robarts Histological Index; NHI, Nancy Histological Index.

‡ Spearman correlation coefficients were used to estimate correlation. $^{**}P < 0.01$

Table 3. Sensitivity, Specificity and Accuracy of Endoscopic Remission in Predicting Histological Remission

	ECAP-HR	RHI-HR	NHI-HR
MES -ER			
sensitivity	30.8%	57.7%	61.5%
specificity	100%	97.3%	100%
accuracy	71.4%	79.4%	84.1%
UCEIS-ER			
sensitivity	44.4%	61.1%	66.7%
specificity	100%	91.1%	91.1%
accuracy	84.1%	82.5%	84.1%
PICASSO-ER			
sensitivity	53.3%	60.0%	73.3%
specificity	100%	87.5%	89.6%

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accuracy	88.9%	81.0%	85.7%

Abbreviations: MES, Mayo Endoscopic Subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PICaSSO, Paddington International Virtual ChromoendoScopy ScOre. HR, histological remission; ER, endoscopic remission

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Figure Legends

Figure 1. Flow chart for the study process.

Figure 2. The representative figures assessed by white-light, iSCAN-2 and iSCAN-3. A-C showed the diffuse ulcer and intramucosal bleeding. D-F showed the diffuse erosion and intramucosal bleeding. G-I showed the mild microerosion with roundish and crowded-tortuous vessels. J-L showed normal mucosal and vascular pattern.

Figure 3. Kaplan-Meier curves for relapse-free survival in patients. (A) MES = 0 vs MES = 1; (B) PICaSSO ≤3 vs PICaSSO >3; (C) UCEIS ≤1 vs UCEIS >1; (D) ECAP ≤4 vs ECAP >4; (E) RHI ≤3 vs RHI >3; (F) NHI ≤1 vs NHI >1; (G) PICaSSO-ER + RHI-HR vs NDR; (H) PICaSSO-ER + ECAP-HR vs NDR; (I) PICaSSO-ER + NHI-HR vs NDR; (J) MES-ER + RHI-HR vs NDR; (K) MES-ER + ECAP-HR vs NDR; (L) MES-ER + NHI-HR vs NDR.

Abbreviations: MES, Mayo Endoscopic Subscore; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PICaSSO, Paddington International Virtual ChromoendoScopy ScOre; ECAP, 'Extension, Chronicity, Activity, Plus additional findings'; RHI, Robarts Histological Index; NHI, Nancy Histological Index.

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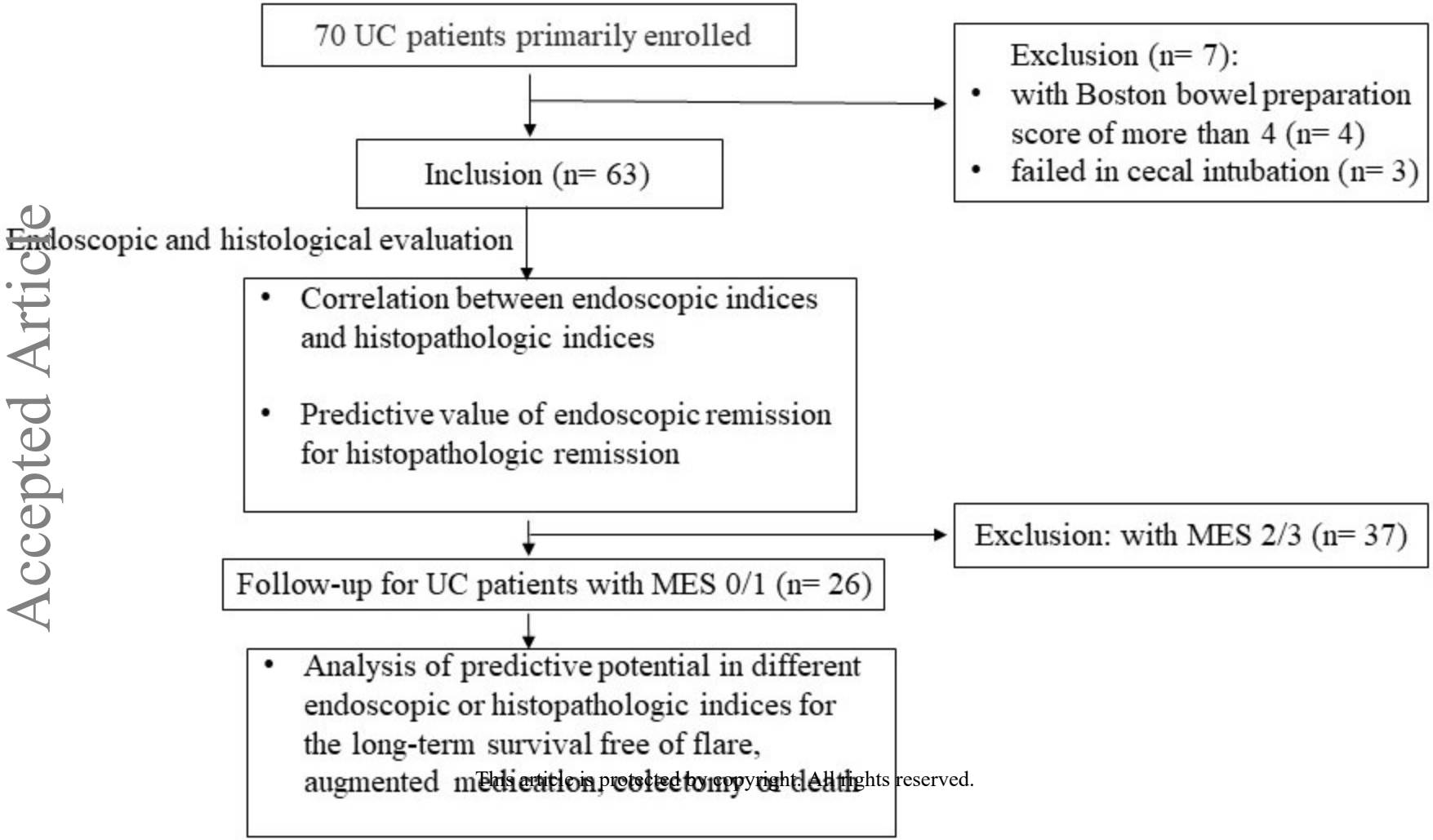

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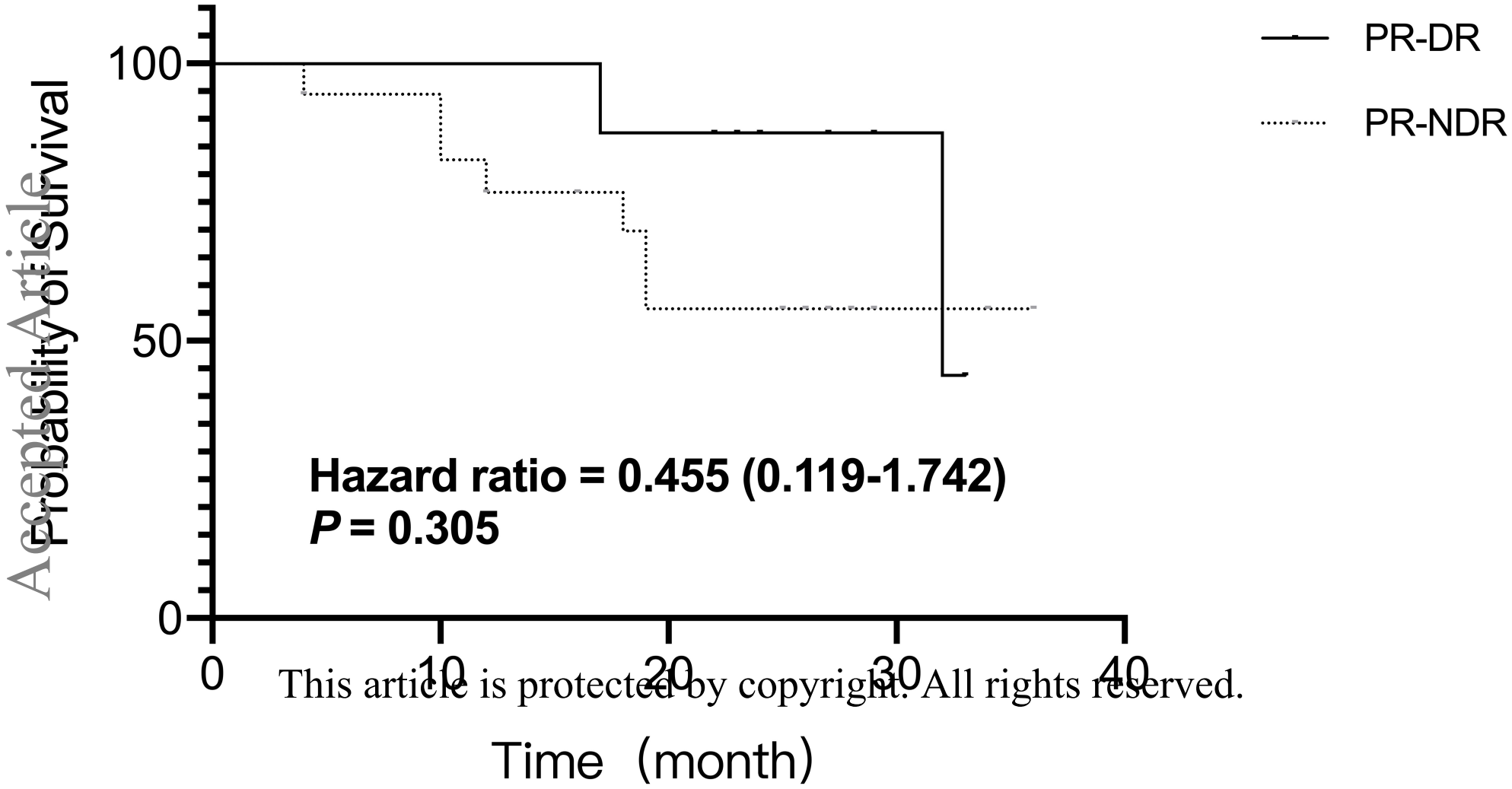

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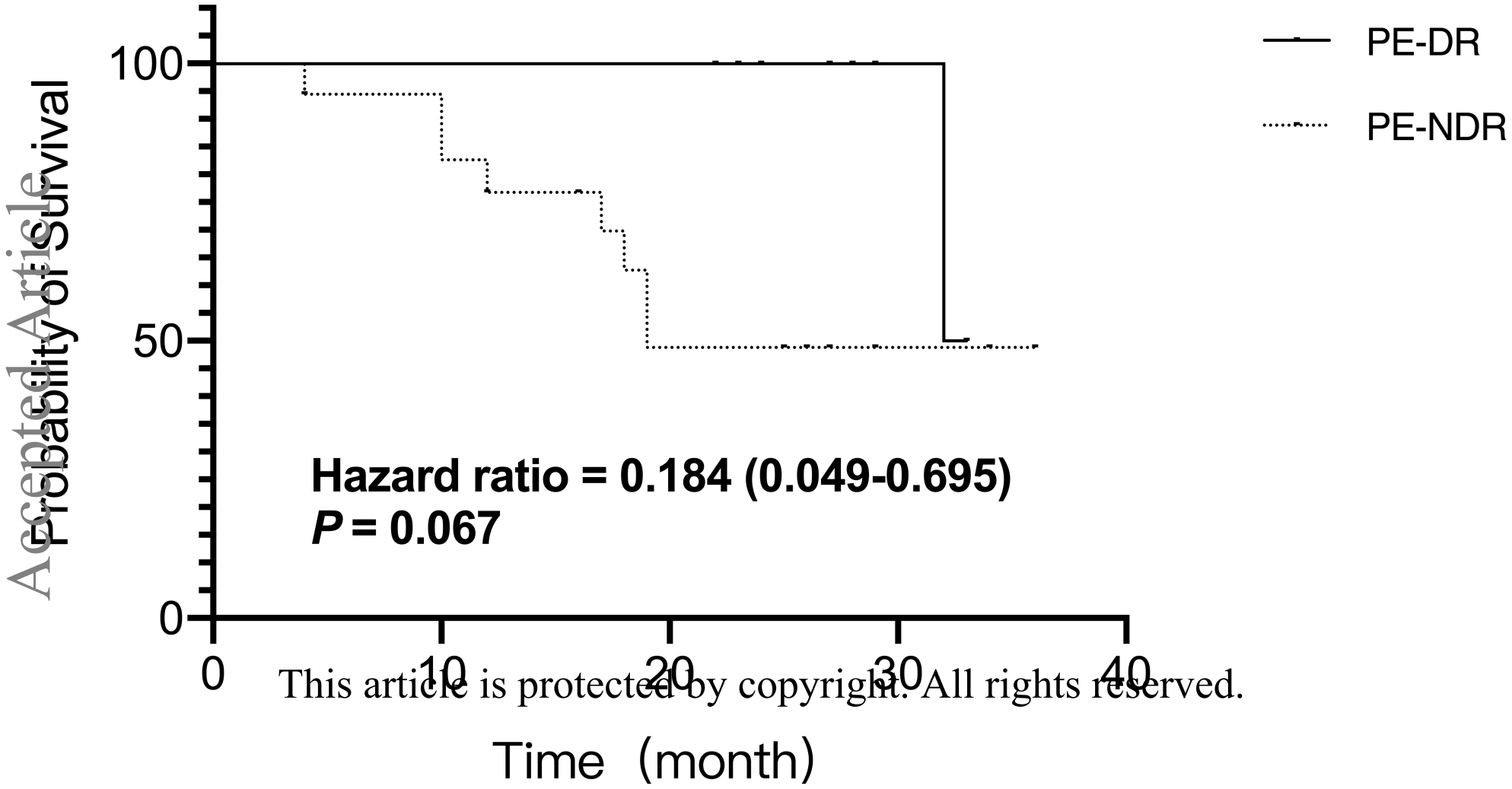

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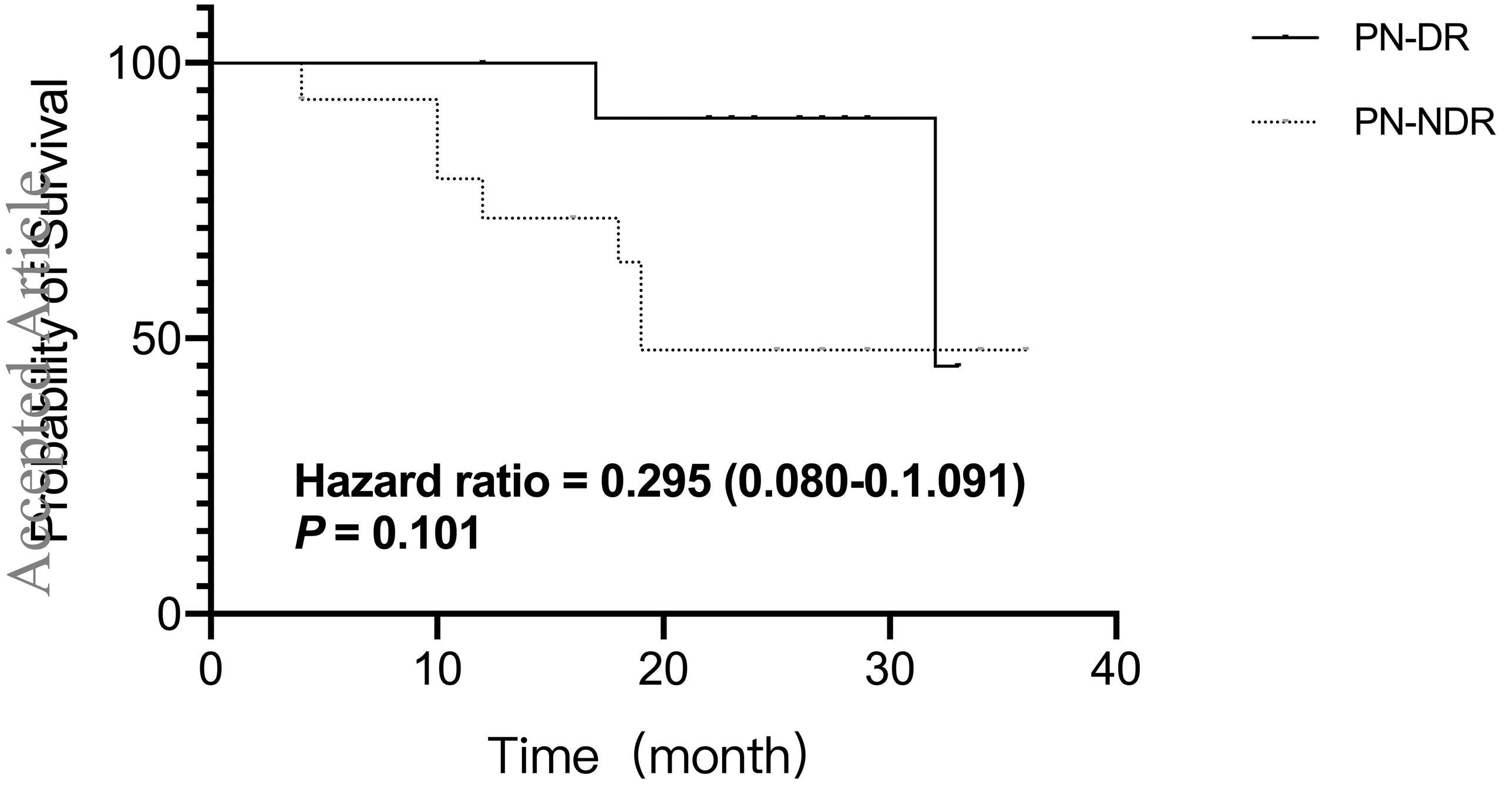

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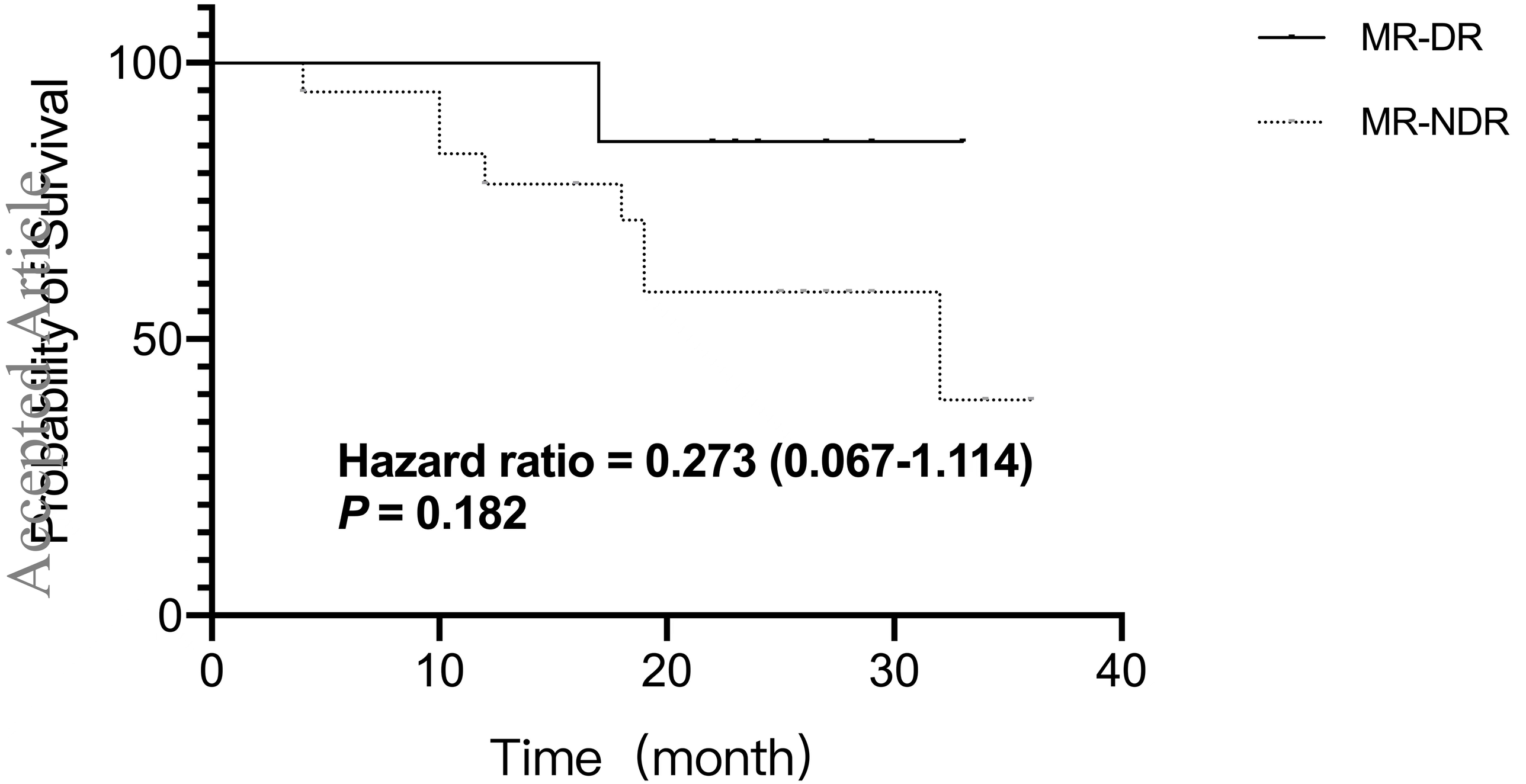

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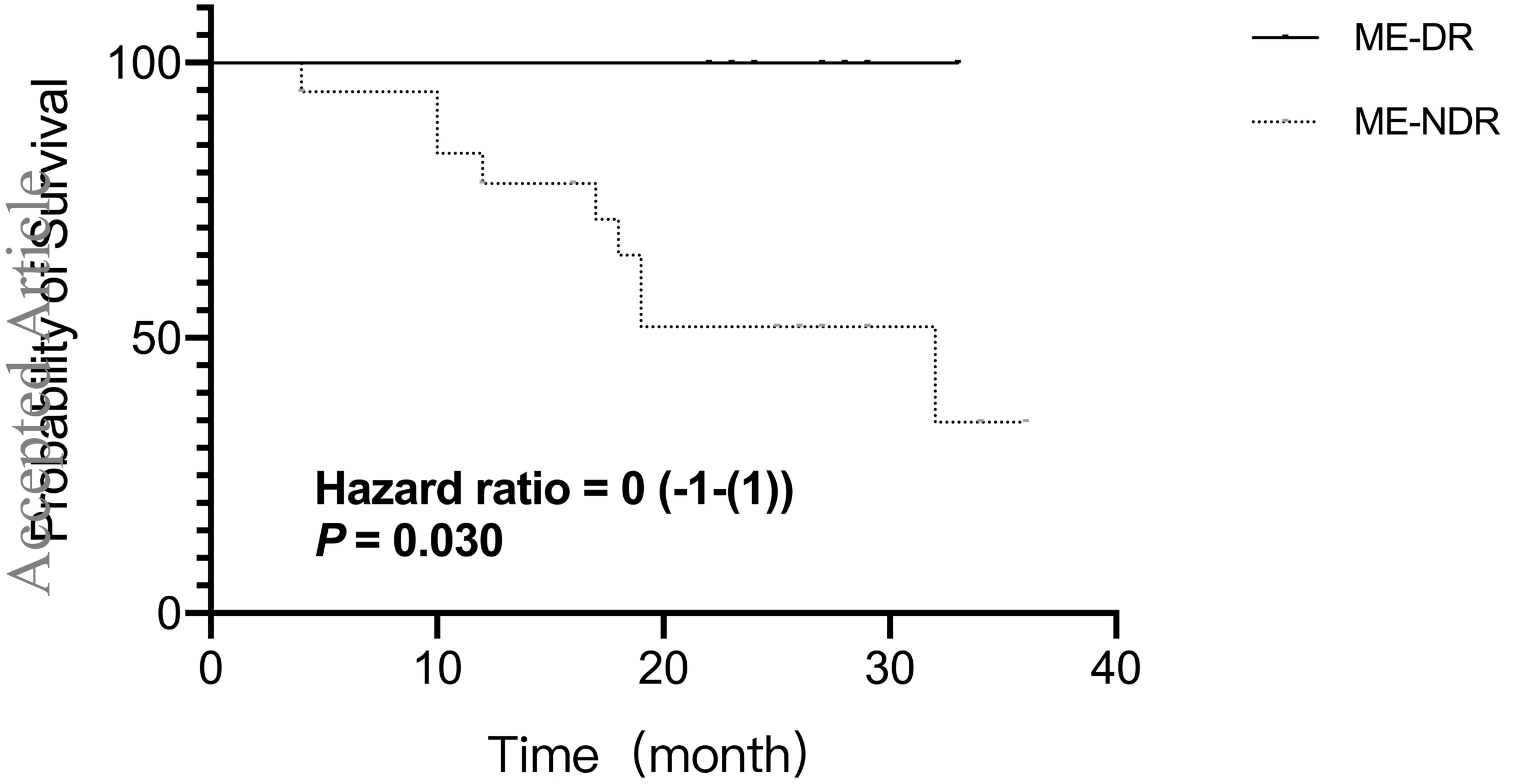

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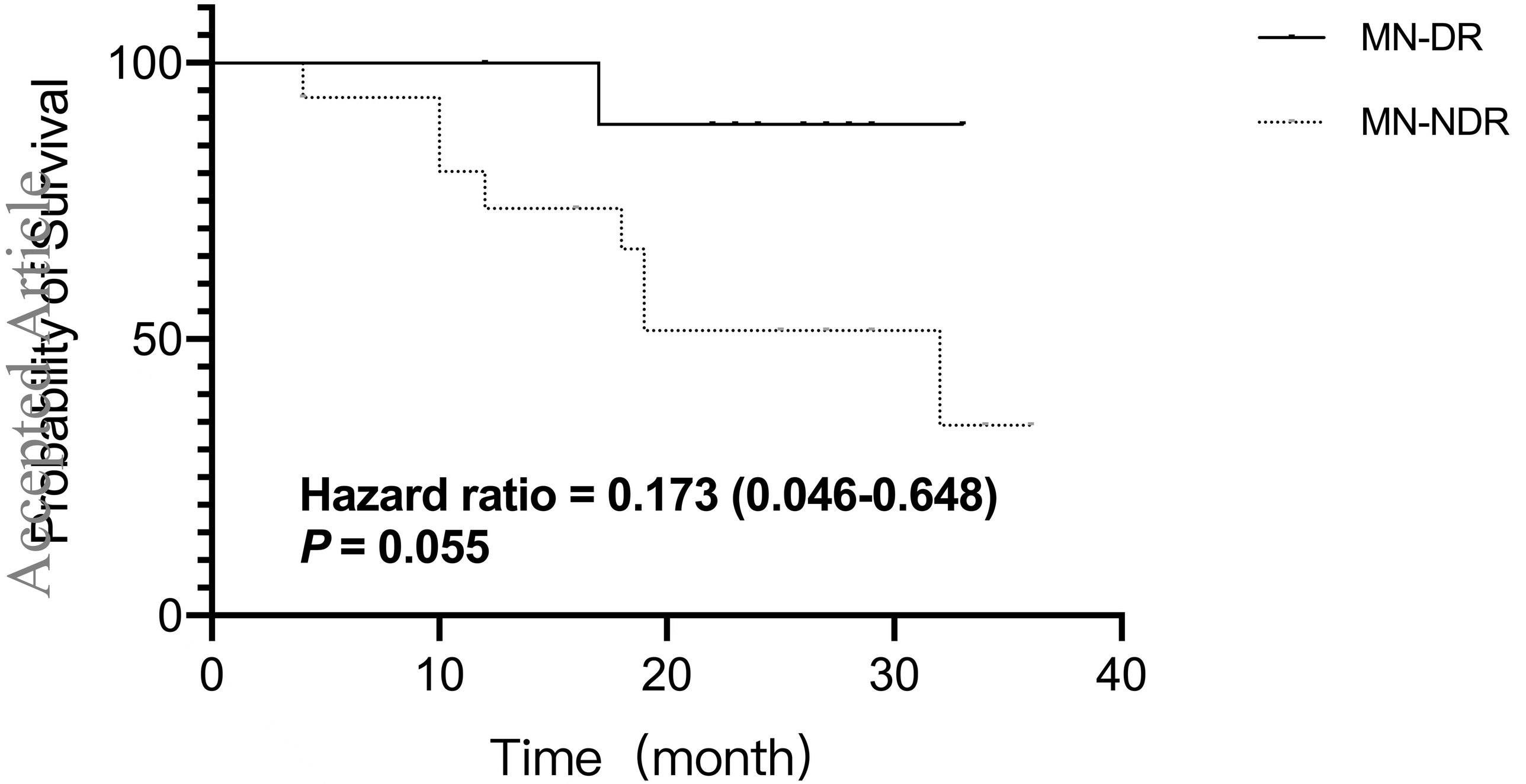

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