

Field-testing the MALT-IPI in a single-center real-world cohort of patients with extranodal marginal zone lymphoma

Vincent Sunder-Plassmann,^{1,2} Barbara Kiesewetter,¹ Ingrid Simonitsch-Klupp,³ Rosa Brand,³ Werner Dolak,⁴ Marius E. Mayerhoefer,^{5,6} and Markus Raderer¹

¹Division of Oncology and ²Christian Doppler Laboratory for Personalized Immunotherapy, Department of Medicine I, Medical University of Vienna, Vienna, Austria; ³Department of Pathology and ⁴Division of Gastroenterology and Hepatology, Department of Medicine III, Medical University of Vienna, Vienna, Austria; ⁵Division of Oncologic Imaging, Department of Radiology, NYU Langone Health, NYU Grossman School of Medicine, New York, NY; and ⁶Department of Biomedical Imaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria

Key Points

- The MALT-IPI does not retain prognostic significance in patients with gastric EMZL or patients managed with *Helicobacter pylori* eradication.
- Autoimmunity does not consistently improve risk stratification beyond the MALT-IPI, but identifies a small subgroup with poor outcomes.

The mucosal-associated lymphoid tissue (MALT)–International Prognostic Index (IPI) is widely applied to estimate outcomes in patients with extranodal marginal zone lymphoma (EMZL) of MALT. Although it was developed in the context of the IELSG-19 trial exclusively in patients treated with chlorambucil, rituximab, or their combination, it is commonly used across virtually all disease settings. However, its applicability beyond contexts resembling the IELSG-19 trial remains debated, and several studies have proposed modifications to improve prognostic precision in EMZL. Here, we retrospectively analyzed 498 patients with newly diagnosed EMZL at the Medical University of Vienna with the dual objective of evaluating the prognostic performance of the MALT-IPI across clinical subgroups, and to assess whether incorporation of autoimmunity could refine risk stratification. Stratification by the MALT-IPI revealed significantly longer progression-free survival (PFS) and overall survival (OS) in patients who were low-risk compared with intermediate- and high-risk groups ($P < .001$) in unselected patients. However, in subgroup analyses, its discriminatory capacity was restricted to patients with extragastric disease, particularly patients with EMZL of the ocular adnexa or the parotid gland or intestinal EMZL, as well as those receiving systemic therapy. On the contrary, patients with gastric EMZL or those managed with *Helicobacter pylori* eradication, local therapy, or watch-and-wait approaches did not derive consistent prognostic separation. Incorporation of autoimmunity identified a small subgroup with inferior PFS and OS, but provided limited incremental prognostic power beyond the established index in most patients. Our results support context-specific applicability of the MALT-IPI, and highlight autoimmunity as a prognostically relevant factor in a small cohort of patients.

Introduction

Extranodal marginal zone lymphoma (EMZL) of mucosal-associated lymphoid tissue (MALT) represents a heterogeneous entity with diverse clinical presentations and management strategies.^{1,2} The recommended first-line therapy in gastric EMZL is upfront *Helicobacter pylori* eradication, which has resulted in unprecedented long-term response rates, due to the strong pathophysiological linkage of

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Data may be made available on reasonable request to the corresponding author, Markus Raderer (markus.raderer@meduniwien.ac.at), contingent upon approval by the institutional review board and completion of a data sharing agreement.

The full-text version of this article contains a data supplement.

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Table 1. Patient characteristics

Characteristic	(N = 498)
Median age (range), y	62 (19-90)
Sex	
Female	286/498 (57.43)
Male	212/498 (42.57)
Primary localization	
Gastric	172/498 (34.54)
Extragastric	326/498 (65.46)
Ocular adnexa	120/326 (36.81)
Lung	53/326 (16.26)
Parotid gland	51/326 (15.64)
Intestinal	24/326 (7.36)
Skin	14/326 (4.29)
Breast	11/326 (3.37)
Thyroid gland	9/326 (2.76)
Salivary glands	7/326 (2.15)
Others (n = 5)	37/326 (11.35)
Stage (Ann Arbor)	
I	283/487 (58.11)
II	90/487 (18.48)
III and IV	114/487 (23.40)
Unknown	11/498 (2.21)
First-line treatment	
Systemic therapy	189/496 (38.10)
Local therapy	124/496 (25.00)
<i>H pylori</i> eradication	135/496 (27.22)
Watchful waiting	38/496 (7.66)
Other	10/496 (2.02)
Unknown	2/498 (0.40)
LDH	
Normal	432/450 (96.00)
Elevated	18/450 (4.00)
Unknown	48/498 (9.64)
MALT-IPI	
Low	216/441 (48.98)
Intermediate	183/441 (41.50)
High	42/441 (9.52)
Unknown	57/498 (11.45)
Median PFS (range), mo	58.72 (0-248.28)
Median OS (range), mo	301.74 (0-367.73)
AD	
Yes	141/453 (31.13)
No	312/453 (68.87)
Unknown	45/498 (9.04)
ANA	
Positive	72/453 (15.89)
Negative	381/453 (84.11)
Unknown	45/498 (9.04)

Table 1 (continued)

Characteristic	(N = 498)
MALT-AD-IPI	
Low	148/419 (35.32)
Intermediate	178/419 (42.48)
High	81/419 (19.33)
Very high	12/419 (2.86)
Unknown	79/498 (15.86)
MALT-ANA-IPI	
Low	182/419 (43.43)
Intermediate	168/419 (40.10)
High	60/419 (14.32)
Very high	9/419 (2.15)
Unknown	79 (15.86)

lymphomagenesis to chronic antigenic stimulation by *H pylori*.³⁻⁵ Although EMZL is generally regarded as an indolent disease with median survival times >12 years,⁶ a subset of patients experience a more aggressive course characterized by early disease progression or relapse.⁷⁻⁹

The MALT–International Prognostic Index (MALT-IPI) is the most widely applied prognostic tool incorporating age (<70 vs ≥70 years), Ann Arbor stage (I-II vs III-IV), and lactate dehydrogenase (LDH; above vs below the upper limit of normal) to stratify patients into low-, intermediate-, and high-risk groups.¹⁰ Although subsequently validated in 3 independent cohorts, the MALT-IPI was originally derived exclusively from patients enrolled in the International Extranodal Lymphoma Study Group (IELSG)-19 trial, who were treated with chlorambucil, rituximab, or their combination.¹¹ Nevertheless, it is routinely used across nearly all disease settings, regardless of therapeutic approach, stage, or lymphoma localization.^{3,9,12} Its applicability beyond contexts resembling the IELSG-19 population remains debated, and several studies have proposed modifications or the incorporation of additional parameters to improve prognostic precision in EMZL.^{13,14} Among these, the concomitant presence of autoimmune disease (AD) appears to be particularly interesting. Although successful *H pylori* eradication eliminates the antigenic drive in gastric EMZL, chronic autoimmune-mediated B-cell stimulation mostly persists despite eradication therapy.^{15,16} Indeed, patients with concomitant AD have demonstrated inferior response to *H pylori* eradication compared with those without AD in a previous study, raising the question whether chronic autoimmune stimuli may be added to the prognostic assessment in EMZL.¹⁷

We have therefore conducted a retrospective analysis of a large, real-world cohort of patients with EMZL, with the objectives of assessing the performance of the MALT-IPI across different therapeutic settings, and exploring whether incorporation of concomitant AD could refine prognostic discrimination beyond the established MALT-IPI.

Materials and methods

Patient characteristics

We have retrospectively analyzed patients with newly diagnosed EMZL managed at the Medical University of Vienna between

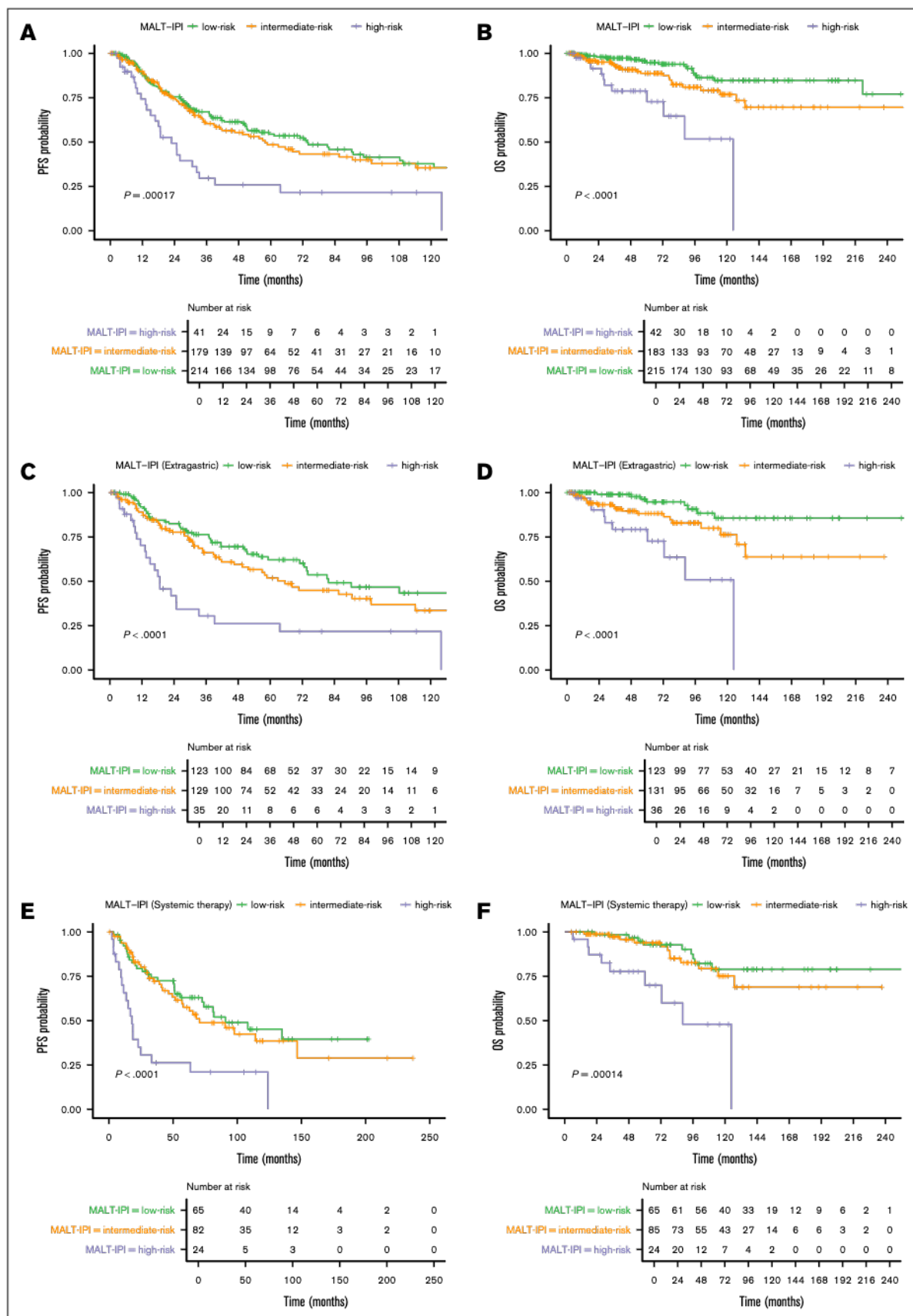


Figure 1.

Table 2. Predictive and prognostic performance of the MALT-IPI in selected clinical subgroups

EMZL subgroup	Median PFS, mo (95 CI)	P value	10-year OS rate, (95 CI)	P value
Gastric EMZL		.935		.333
Low-risk	49.2 (29.4-109.4)		83.5 (72.8-95.8)	
Intermediate-risk	34.2 (24.9-NR)		76.9 (61.9-95.5)	
High-risk	31.5 (26.0-NR)		NR	
Extragastric EMZL		<.001		<.001
Low-risk	81.8 (72.7-NR)		85.7 (76.5-96.0)	
Intermediate-risk	65.5 (49.5-114.3)		76.3 (65.4-89.0)	
High-risk	18.7 (13.6-39.1)		50.9 (28.8-90.0)	
EMZL of the ocular adnexa		.036		.004
Low-risk	71.0 (50.0-NR)		91.8 (81.5-100.0)	
Intermediate-risk	70.7 (33.1-NR)		82.5 (70.1-97.0)	
High-risk	24.8 (9.5-NR)		66.7 (42.0-100.0)	
EMZL of the parotid gland		.034		<.001
Low-risk	48.2 (22.1-NR)		85.6 (68.8-100.0)	
Intermediate-risk	68.2 (41.0-NR)		87.7 (72.8-100.0)	
High-risk	16.8 (5.4-NR)		NR	
Pulmonary EMZL		.442		.768
Low-risk	NA (74.0-NR)		75.0 (49.6-100.0)	
Intermediate-risk	97.7 (38.7-NR)		NR	
High-risk	39.1 (15.1-NR)		NR	
Intestinal EMZL		.013		.311
Low-risk	134.9 (NR-NR)		100.0 (100.0-100.0)	
Intermediate-risk	27.9 (27.9-NR)		NR	
High-risk	13.2 (NR-NR)		NR	
Stage I/II EMZL		.606		.003
Low-risk	73.6 (51.4-109.4)		84.7 (77.6-92.5)	
Intermediate-risk	57.9 (38.7-114.3)		69.4 (56.4-85.3)	
High-risk	30.6 (22.9-NR)		NR	
Stage III/IV EMZL		.001		<.001
Intermediate-risk	65.5 (34.8-NR)		86.2 (76.1-97.6)	
High-risk	18.7 (13.6-39.1)		49.9 (28.5-87.5)	

CI, confidence interval; EMZL, extranodal marginal zone lymphoma; NR, not reached; OS, overall survival; PFS, progression-free survival.
 Bold value indicates significant results ($P < .05$).

January 1999 and December 2024. Clinical data were retrieved from patient records, and disease staging was performed according to the modified Ann Arbor classification.¹⁸ Histological diagnoses were (re-)evaluated by a reference hematopathologist according to the current World Health Organization classification criteria for EMZL of MALT.¹ The MALT-IPI was calculated based on age ≥ 70 years, stage III/IV disease, and elevated LDH, as previously published.¹⁰ Subgroup analysis of the predictive and prognostic performance of the MALT-IPI was performed according to primary EMZL localization, EMZL stage, and first-line therapy. Given the

speculated impact of autoimmune conditions on the clinical course of patients with EMZL, we aimed to explore whether incorporation of autoimmunity, captured here as the concomitant presence of AD or antinuclear antibody (ANA) seropositivity, could refine predictive or prognostic discrimination of the MALT-IPI. We have therefore exploratorily constructed the “MALT-AD-IPI” and the “MALT-ANA-IPI” by expanding the MALT-IPI by 1 additional point for the presence of AD or ANA seropositivity as a fourth variable (low-risk = 0 points, intermediate-risk = 1 point, high-risk = 2 points, very high-risk ≥ 3 points). This study was approved by the ethics committee

Figure 1. Predictive and prognostic performance of the MALT-IPI across clinical subgroups of patients with EMZL. Kaplan-Meier curves for PFS (A,C,E) and OS (B,D,F) according to risk group assignment by the classical MALT-IPI in our overall cohort (A-B), patients with extragastric EMZL (C-D), and patients with EMZL who were treated with upfront systemic therapy (E-F). Patients were stratified into low-, intermediate-, and high-risk groups according to the MALT-IPI. Comparative statistical analysis was performed using log-rank tests.

of the Medical University of Vienna (EC approval number: 791/2011). Due to the retrospective nature of this study, individual informed consent was waived by the ethics committee.

Statistical analysis

Progression-free survival (PFS) and overall survival (OS) were estimated by Kaplan-Meier analysis and compared using the log-rank test. PFS was defined as the time from diagnosis to progression, relapse, or death. OS was defined as the time from diagnosis to death of any cause. Patients without events were censored for OS and PFS analysis at their respective last clinical follow-up. For each risk-scoring tool, subgroup analyses were performed according to primary lymphoma localization (ie, gastric and extragastric EMZL) and by first-line treatment strategy (ie, systemic therapy, *H pylori* eradication, local therapy, or watchful waiting). A 2-sided *P* value of $<.05$ was considered statistically significant for all analyses.

Results

Patient characteristics

In total, 498 patients with EMZL were analyzed (Table 1). The median age at diagnosis was 62 years (range, 19-90), and 286 of 498 (57.4%) patients were female. Although 172 of 498 (34.5%) patients had primary gastric EMZL, 326 of 498 (65.5%) patients had primary extragastric disease. Among those, EMZL was predominantly located in the ocular adnexa (120/326, 36.81%), the lung (53/326, 16.26%), the parotid gland (51/326, 15.64%), or the intestine (24/326, 7.36%). Most patients had Ann Arbor stage I or II disease (373/487, 76.6%; *n* = 11 unknown), whereas 114 of 487 (23.4%) were diagnosed with stage III or IV lymphoma. Systemic therapy was the first-line treatment in 189 of 496 (38.1%) patients (*n* = 2 unknown), whereas 135 of 496 (27.22%) patients received upfront *H pylori* eradication and 124 of 496 (25.0%) received local therapy including radiotherapy or surgery. An additional 38 of 496 (7.66%) patients were managed with "watchful waiting." The median PFS and OS in our cohort were 58.73 months (range, 0-248.28) and 301.74 months (range, 0-367.73), respectively.

Prognostic performance of the MALT-IPI in patients with EMZL

The MALT-IPI could be calculated for 441 of 498 (90.0%) patients, and was low in 216 of 441 (49.0%), intermediate in 183 of 441 (41.5%), and high in 42 of 441 (9.5%). Kaplan-Meier analysis demonstrated superior PFS among patients with low-risk MALT-IPI (median PFS = 73.64 months [95% confidence interval (CI), 51.39-109.45]) compared with patients in intermediate- (median PFS = 57.90 months [95% CI, 41.00-97.71]) and high-risk groups (22.88 months [95% CI, 16.77-39.12]; $P < .001$; Figure 1A). Similarly, OS was significantly longer in patients within the low-risk group ($P < .001$; Figure 1B). The 10-year OS rate in patients in the low-risk group was 84.7% (95% CI, 77.6-92.5) compared with 76.8% (95% CI, 68.0-86.7) for intermediate-risk and 51.7% (95% CI, 29.9-89.6) for high-risk groups ($P < .001$). These findings confirm the prognostic utility of the MALT-IPI in primarily unselected real-world patients with EMZL, and suggest a representative patient collective in our analysis.

Subgroup analysis of the prognostic performance of the MALT-IPI

We next explored the predictive and prognostic power of the MALT-IPI in selected clinical subgroups. Although the score retained prognostic value in the overall cohort, its discriminative capacity was more nuanced when stratified by clinical subgroups.

Prognostic performance of the MALT IPI according to primary EMZL localization. Upon stratification of our cohort into patients with primary gastric EMZL and primary extragastric EMZL, the MALT-IPI largely retained predictive and prognostic significance in patients with primary extragastric EMZL (Figure 1C-D; Table 2). The median PFS was 81.8 months (95% CI, 72.7-not reached (NR)) in low-risk, 65.5 months (95% CI, 49.5-114.3) in intermediate-risk, and 18.7 months (95% CI, 13.6-39.1) in high-risk extragastric EMZL, with 10-year OS rates of 85.7% (95% CI, 76.5-96.0), 76.3% (95% CI, 65.4-89.0), and 50.9% (95% CI, 28.8-90.0), respectively (log-rank $P < .001$ each). Upon stratification of our cohort into individual extragastric anatomical primary localizations, the MALT-IPI retained its predictive and prognostic performance in patients with EMZL of the ocular adnexa and the parotid gland (log rank $P < .05$ each; Figure 2A-D). In patients with intestinal EMZL, the median PFS was significantly shorter in patients with high-risk EMZL (log-rank $P = .013$; Figure 2E), but OS did not show statistically significant differences between MALT-IPI risk groups ($P > .05$; Figure 2F). In patients with primary pulmonary EMZL, neither PFS nor OS differed between MALT-IPI risk groups (log-rank $P > .05$ each; Figure 2G-H), although analysis was certainly limited by sample size in individual localizations. In patients with primary gastric EMZL, neither PFS nor OS showed significant differences between risk groups (log-rank $P > .05$ each; Figure 3A-B).

Prognostic performance of the MALT IPI according to first line therapy. As for extragastric primary EMZL localization, the MALT-IPI retained its prognostic value in patients receiving upfront systemic therapy (Figure 1E-F). In this subgroup, median PFS ranged from 90.8 months (95% CI, 72.7-NR) for patients in the low-risk group to 18.0 months (95% CI, 11.4-63.6) for patients in the high-risk group, and 10-year OS rates were 78.9% (95% CI, 67.2-92.7), 75.2% (95% CI, 62.5-90.4), and 47.9% (95% CI, 26.0-88.5) across the 3 strata (log-rank $P < .001$ each).

However, in patients treated with local therapy (radiotherapy or surgery; Figure 3C-D), upfront *H pylori* eradication (Figure 3E-F), or watchful waiting (Figure 3G-H), neither PFS nor OS showed significant differences between risk groups, with the exception of OS in patients treated with local therapy (log-rank $P = .00019$). PFS and OS in the remaining groups were largely overlapping across all MALT-IPI strata (log-rank $P > .05$), underscoring the limited applicability of the score in these clinical settings.

Prognostic performance of the MALT IPI in patients with stage I/II or III/IV EMZL. We next analyzed the performance of the MALT-IPI according to EMZL stage. In patients with stage I/II EMZL, no PFS benefit of patients with low-risk MALT-IPI was observed (Figure 4A; log-rank $P = .67$). However, patients with intermediate-risk MALT-IPI had significantly shorter OS than patients with low-risk MALT-IPI (Figure 4B; log-rank $P = .003$).

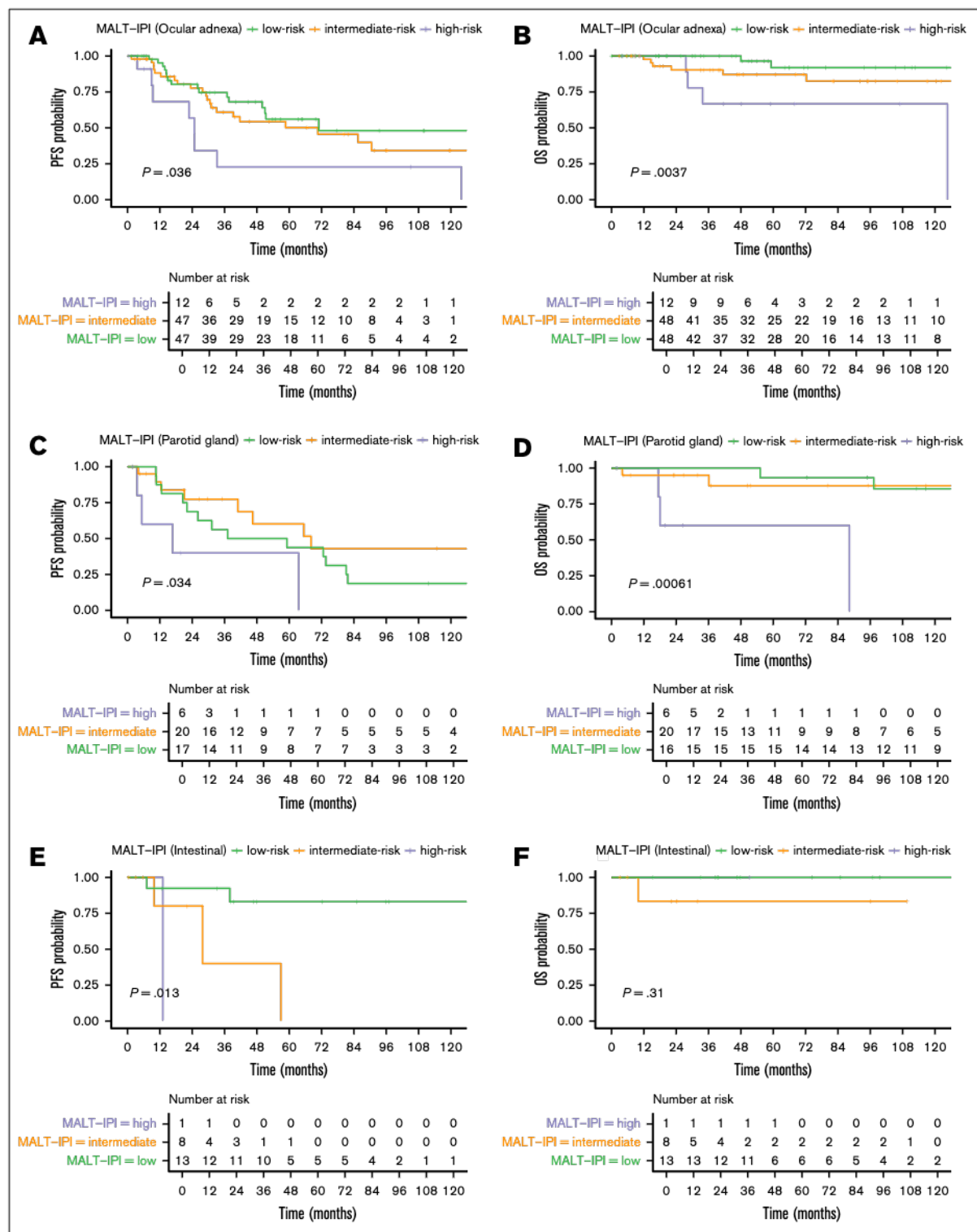


Figure 2. Predictive and prognostic performance of the MALT-IPI across distinct extragastric anatomical EMZL localizations. Kaplan-Meier curves for PFS (A,C,E,G) and OS (B,D,F,H) according to distinct extragastric EMZL localization. (A-B) Patients with EMZL in the ocular adnexa. (C-D) Primary EMZL localization in the parotid gland. (E-F) Primary intestinal EMZL. (G-H) Primary pulmonary EMZL.

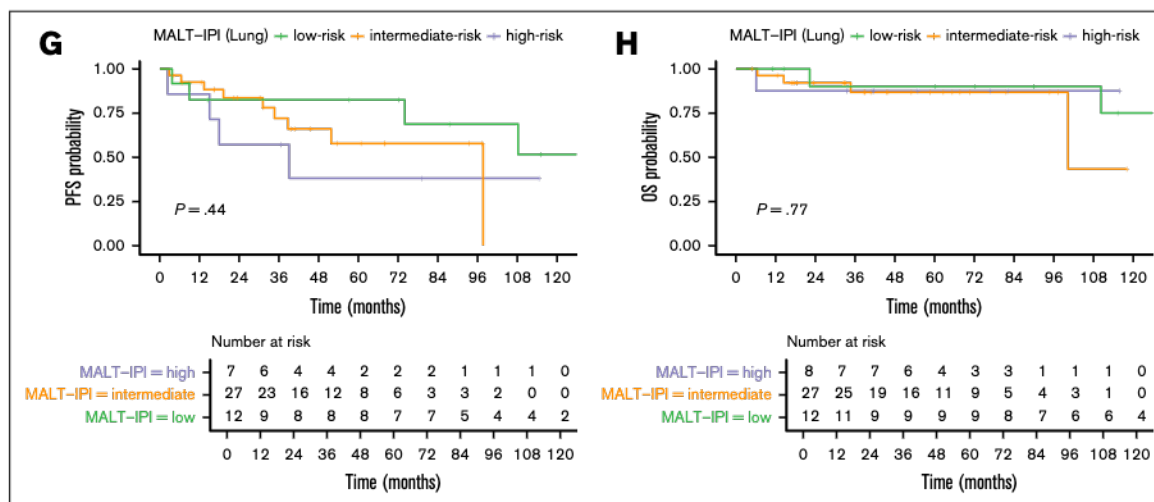


Figure 2 (continued)

Interestingly, although certainly limited by sample size ($n = 6$), patients with high-risk stage I/II EMZL had longer OS than patients in low- and high-risk groups. In patients with stage III/IV EMZL, patients in the high-risk group had significantly shorter OS and PFS than patients in the intermediate-risk group (log rank $P = .0012$ and $<.0001$; Figure 4C-D). Given the fact that having stage III/IV EMZL precludes categorization as low-risk in the MALT-IPI, patients in the low-risk group were absent in stage III/IV EMZL (Table 2).

Incorporation of autoimmunity into the MALT-IPI does not significantly improve prognostication of patients with EMZL

Information on the presence of concomitant AD was available for 419 of 498 (84.1%) patients. Of those, 141 of 419 (31.1%) had a concomitant AD. The ANA serostatus was assessed in 453 of 498 (91.0%) patients, of whom 72 of 453 (15.9%) were seropositive. Thus, 148 patients were classified as low-risk, 178 as intermediate-risk, 81 as high-risk, and 12 as very high-risk according to the exploratory MALT-AD-IPI. The MALT-AD-IPI could not be calculated in 79 of 498 patients (15.9%) due to missing data. According to the MALT-ANA-IPI, 182 of 419 patients (43.4%) were classified as low-risk, 168 of 419 (40.1%) as intermediate-risk, 60 (14.3%) as high-risk, and 9 of 419 (2.2%) as very high-risk ($n = 79$ not available (NA); Table 1). In our cohort, no significant difference in the first-line treatment strategy was noted comparing patients with and without either autoimmunological parameter ($P > .05$ each).

The addition of either AD (MALT-AD-IPI) or ANA seropositivity (MALT-ANA-IPI) resulted in risk group stratifications that were broadly comparable to the classical MALT-IPI (Table 3). In the MALT-AD-IPI, the median PFS was 18.7 months (95% CI, 15.1-NR) in the very high-risk group, compared with 46.5 months (95% CI, 30.6-NR) in high-risk, 62.9 months (95% CI, 49.5-90.3) in intermediate-risk, and 71.0 months (95% CI, 50.4-121.1) in low-risk groups (log-rank $P < .001$; supplemental Figure 1A). Although median PFS times suggest promising risk-group separation, Kaplan-Meier analysis revealed no clear separation of low-, intermediate-, and high-risk groups. Similarly, the MALT-ANA-IPI

identified a very high-risk group with a median PFS of 16.8 months (5.4-NR), compared with 41.8 months (95% CI, 32.3-NR) in high-risk, 57.9 months (95% CI, 37.2-82.8) in intermediate-risk, and 74.0 months (95% CI, 51.1-134.9) in low-risk groups (log-rank $P < .001$; supplemental Figure 1B). However, Kaplan-Meier analysis revealed no clear separation of patients in the intermediate- and high-risk groups.

Comparable results were obtained for OS. In the MALT-AD-IPI, 10-year OS rates were 89.6% (95% CI, 81.6-98.3) in low-risk, 76.7% (95% CI, 67.4-87.2) in intermediate-risk, 80.5% (95% CI, 68.6-94.5) in high-risk, and 34.3% (95% CI, 12.4-94.6) in very high-risk groups (log-rank $P < .001$; supplemental Figure 1C). The MALT-ANA-IPI showed similar stratification, with 10-year OS rates of 87.2% (95% CI, 79.5-95.7), 78.3% (95% CI, 69.6-88.1), 75.0% (95% CI, 58.3-96.3), and 22.2% (95% CI, 4.2-100.0) for patients in the low-, intermediate-, high-, and very high-risk groups, respectively (log-rank $P < .001$; supplemental Figure 1D). However, similar to PFS, the apparent stepwise decrease in median OS did not translate into clearly separated survival curves.

Discussion

The present analysis provides an in-depth evaluation of the prognostic and predictive utility of the MALT-IPI in a large, real-world cohort of patients with EMZL. Although the MALT-IPI remains the most widely applied risk stratification tool in EMZL, its derivation from a single, trial-based population and treatment context has raised concerns about its generalizability.¹⁰ By systematically assessing its performance across clinical subgroups and exploring autoimmune-based modifications, our findings demonstrate both the strengths and the limitations of the score in contemporary practice.

In the overall cohort, the MALT-IPI retained significant prognostic discrimination for both PFS and OS, confirming its validity in unselected patients. However, its performance was heterogeneous across clinical contexts. Specifically, the index demonstrated robust predictive and prognostic power among patients with extragastric EMZL, particularly in patients with EMZL of the

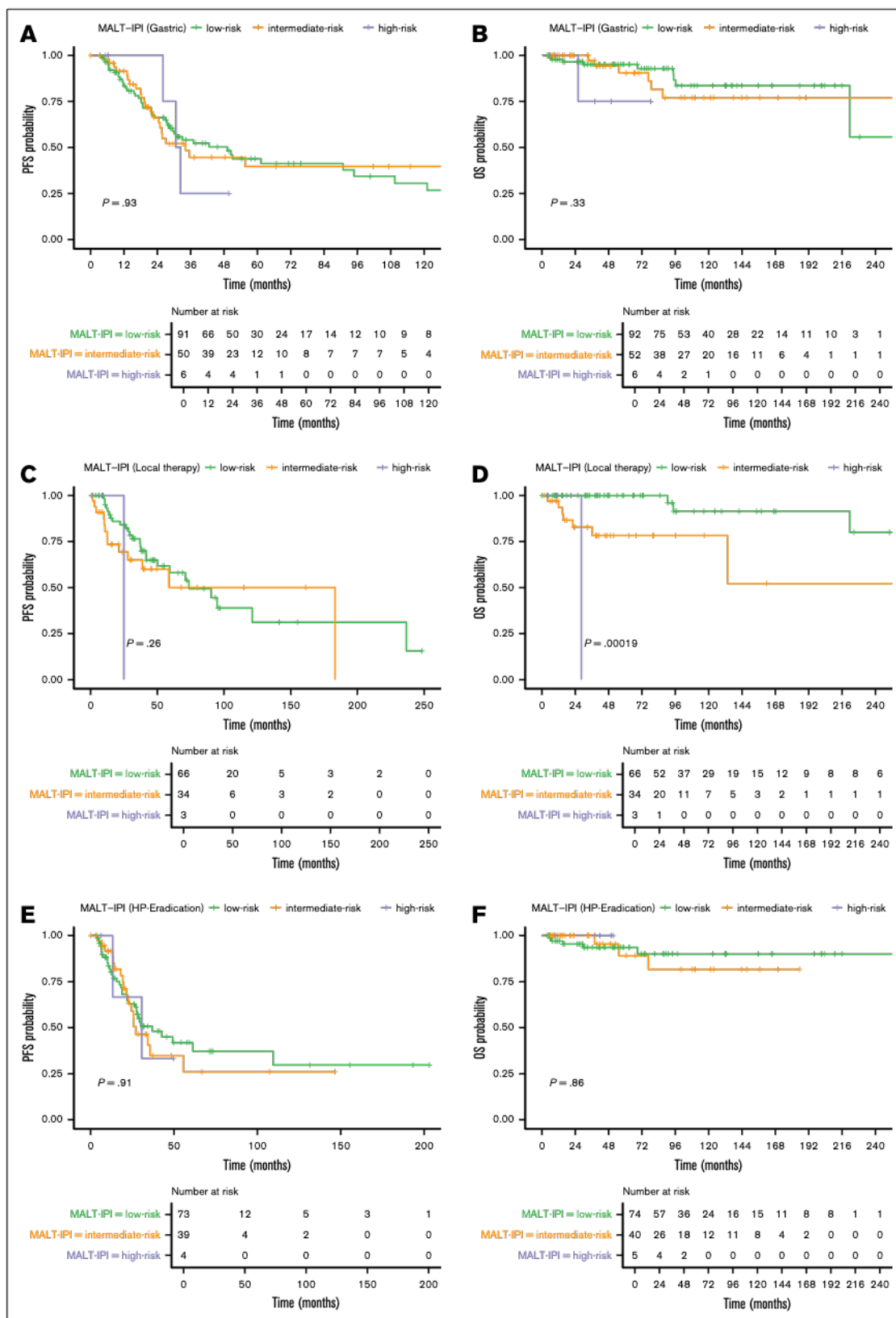


Figure 3. Predictive and prognostic performance of the MALT-IPI across clinical subgroups of patients with EMZL. Kaplan-Meier curves for PFS (A,C,E,G) and OS (B,D,F,H) according to risk group assignment by the classical MALT-IPI in patients with gastric EMZL (A-B), patients treated with upfront local therapy (C-D), patients treated with upfront *H pylori* eradication (E-F), and patients managed with upfront watchful waiting (G-H). Patients were stratified into low-, intermediate-, and high-risk groups according to the MALT-IPI. Comparative statistical analysis was performed using log-rank tests.

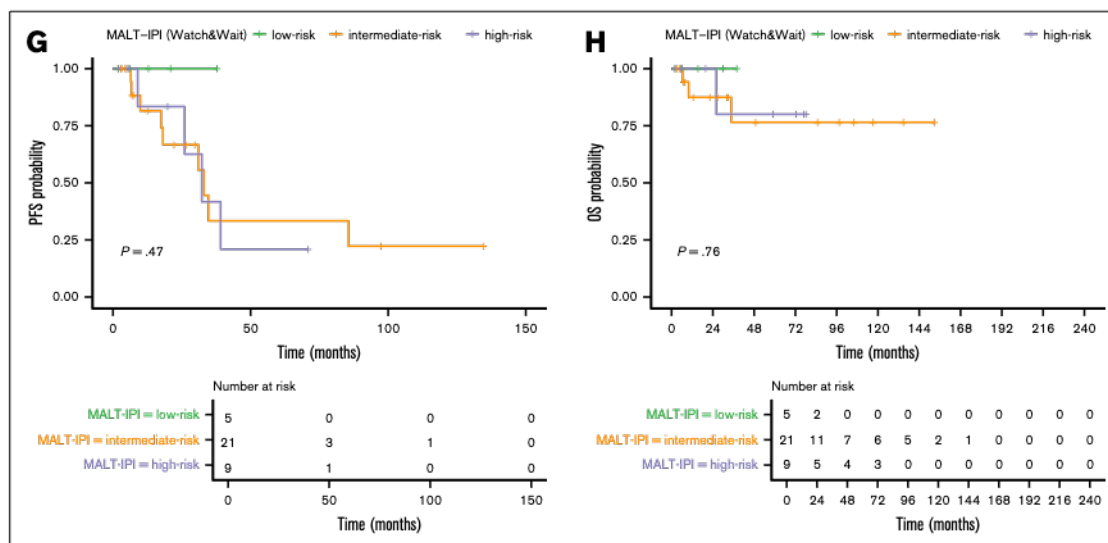


Figure 3 (continued)

ocular adnexa or the parotid gland, as well as in patients with primary intestinal EMZL, whereas no consistent separation of risk groups was observed among patients with primary gastric EMZL. With regard to first-line treatment, the MALT-IPI retained predictive and prognostic power in patients treated with systemic therapy, but not in patients treated with upfront *H pylori* eradication or in patients that were initially managed with watchful waiting. Interestingly, although we did not observe clear risk-group separation in the PFS of patients treated with upfront local therapy, OS was progressively decreasing with increasing MALT-IPI in this cohort. These findings are highly consistent with the clinical and biological context in which the MALT-IPI was originally derived, the IELSG-19 trial, in which patients received chlorambucil, rituximab, or their combination.¹¹ The retained performance in extragastric and systemically treated cohorts thus likely reflects similarity to the trial's population and therapeutic setting.

By contrast, gastric EMZL, historically the first to be consistently managed with *H pylori* eradication or localized radiotherapy, represents a biologically distinct and clinically more indolent subgroup.^{2,7} In these patients, prognosis may be predominantly driven by local response to bacterial eradication (ie, the removal of the antigenic stimulus), and persistent antigenic pressure in cases refractory to eradication that might not be captured by systemic parameters such as elevated LDH or advanced age. Indeed, *H pylori* eradication alone induces regression in a high proportion of patients with EMZL, whereas failure is associated with deeper invasion, *H pylori*-negative status, or chromosomal translocations such as t(11;18) that confer antigen independence.^{4,19,20}

Consequently, the conventional MALT-IPI, which emphasizes systemic disease burden, failed to capture the major prognostic determinants in patients with primary gastric EMZL in our cohort. The same held true for patients managed with *H pylori* eradication, in whom PFS and OS curves largely overlapped across MALT-IPI strata. Previous studies proposing adaptations or refinements of the MALT-IPI, including the recently developed Revised MALT-IPI, have aimed to enhance prognostic precision by incorporating

disease-specific parameters, such as involvement of multiple mucosal sites, though their applicability in routine clinical practice remains to be defined.^{13,21} Unfortunately, data on multiple mucosal sites were not consistently available in our cohort, reflecting the retrospective nature of data collection dating back to 1999, which precluded direct comparison of our findings to the Revised MALT-IPI.

Given the well-established association between chronic immune stimulation and the pathogenesis of EMZL, we have evaluated whether incorporation of AD or ANA seropositivity could refine prognostic discrimination. Overall, both extended indices generated risk groups broadly comparable to those of the classical MALT-IPI, but identified a small subset of patients with particularly poor outcomes. The median PFS and OS in these patients were shorter than in patients in the high-risk group of the classical index, supporting the notion that chronic autoimmune activation may promote treatment-resistant disease biology.

However, outside of this subgroup, neither modification substantially improved the overall prognostic performance. In both the MALT-AD-IPI and MALT-ANA-IPI, outcomes in the low- and intermediate-risk groups were comparable to those of the original index, and patients in the high-risk group often overlapped with patients in the intermediate-risk group of the classical score. Although median PFS and 10-year OS rates suggested some added value of incorporation of autoimmunity into the prognostic assessment, Kaplan-Meier curves did not demonstrate consistent additional separation between risk groups. Of note, the upfront treatment choice between patients with and without concomitant autoimmunity did not differ significantly in our cohort, suggesting that concomitant autoimmunity was largely not considered a treatment-deciding parameter. These results suggest that, although autoimmunity and ANA positivity may identify biologically distinct patients with adverse features, their inclusion alone does not meaningfully enhance population-level risk stratification. From a biological perspective, these findings are intuitive. In *H pylori*-driven EMZL, eradication of the underlying antigenic trigger often leads to durable remission. In contrast, autoimmune-mediated

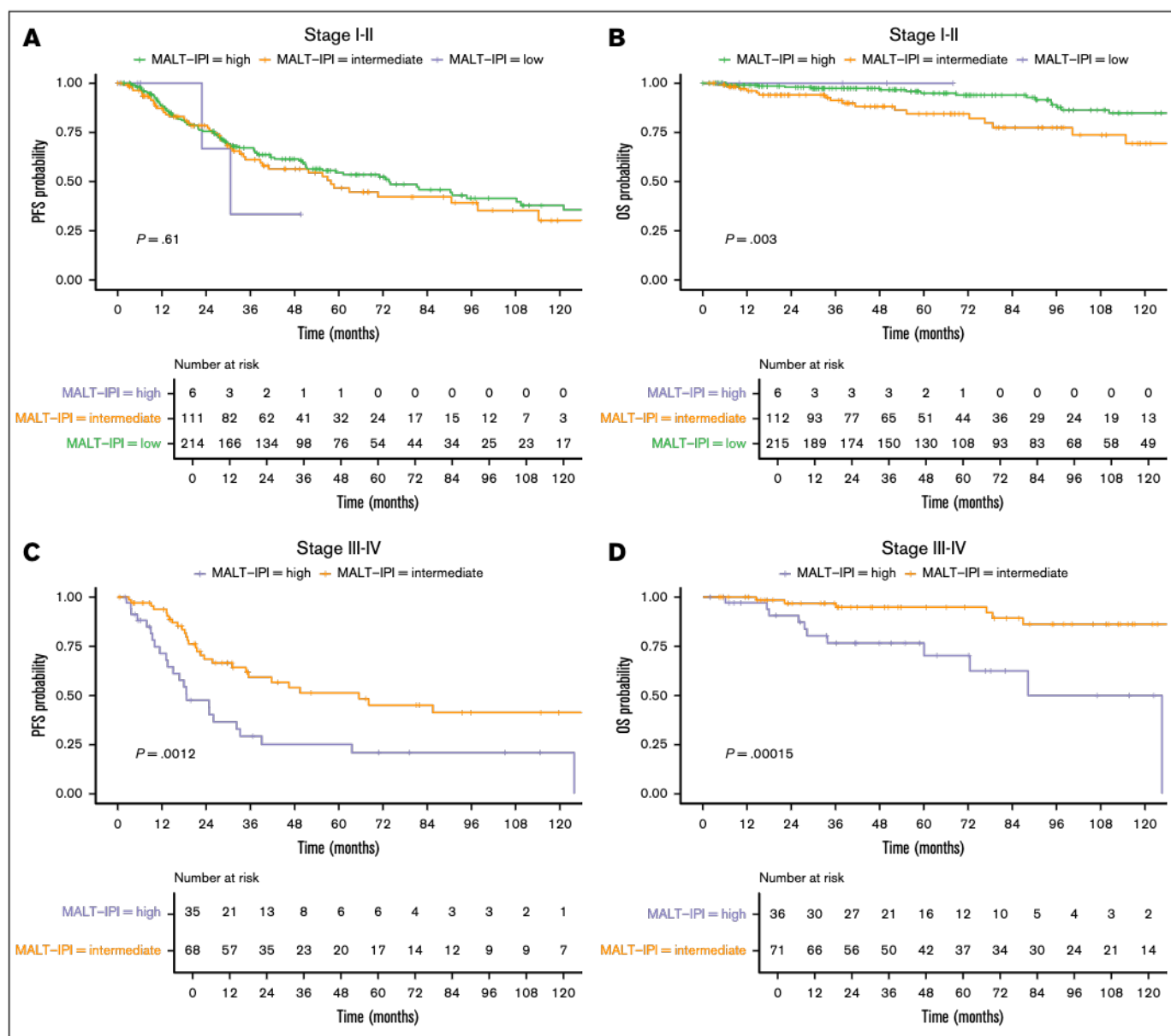


Figure 4. Predictive and prognostic performance of the MALT-IPI in patients with stage I/II vs III/IV EMZL. Kaplan-Meier curves of patients with stage I/II EMZL (PFS, A; OS, B) and stage III/IV EMZL (PFS, C; OS, D).

antigenic stimulation represents a persistent, systemic driver of B-cell proliferation and survival, which cannot be eliminated by local or anti-infective therapy, and may foster refractory or aggressive disease.^{15,16} The potential prognostic relevance of autoimmunity and ANA seropositivity underscores the interplay between chronic immune stimulation and lymphoma persistence. Indeed, previous studies have shown that patients with autoimmune comorbidities, particularly Sjögren syndrome or Hashimoto thyroiditis, exhibit inferior responses to *H pylori* eradication and are more likely to require systemic treatment.¹⁷

Although our data suggest that the presence of autoimmune phenomena may identify a small group of particularly vulnerable

patients, these parameters alone appear to be insufficient to refine global prognostic stratification, and interpretation of these findings warrants caution. The number of patients identified as very high-risk was small in both indices ($n = 9$ and $n = 12$ in the MALT-AD-IPI and MALT-ANA-IPI, respectively), and the assessment of autoimmunity was not uniformly performed across the entire study period. Future studies using standardized definitions and larger, independent data sets will be required to validate the prognostic impact of autoimmune status, and to determine whether incorporation of composite immunologic markers may provide more robust discrimination. In the future, incorporation of composite immune signatures may better capture the impact of systemic immune activation on EMZL outcomes.

Table 3. Predictive and prognostic performance of the MALT-IPI and the exploratory MALT-AD-IPI and MALT-ANA-IPI in patients with EMZL

Prognostic model	Median PFS, mo (95 CI)	P value	10-year OS rate, (95 CI)	P value
MALT-IPI		<.001		<.001
Low-risk	73.6 (51.4-109.4)		84.7 (77.6-92.5)	
Intermediate-risk	57.9 (41.0-97.7)		76.8 (68.0-86.7)	
High-risk	22.9 (16.8-39.1)		51.7 (29.9-89.6)	
MALT-AD-IPI		<.001		<.001
Low-risk	71.0 (50.4-121.1)		89.6 (81.6-98.3)	
Intermediate-risk	52.9 (49.5-90.3)		76.7 (67.4-87.2)	
High-risk	46.5 (30.6-NR)		80.5 (68.6-94.5)	
Very high-risk	18.7 (15.1-NR)		34.3 (12.4-94.6)	
MALT-ANA-IPI		<.001		<.001
Low-risk	74.0 (51.1-134.9)		87.2 (79.5-95.7)	
Intermediate-risk	57.9 (37.2-81.8)		78.3 (69.6-88.1)	
High-risk	41.8 (32.3-NR)		75.0 (58.3-96.3)	
Very high-risk	16.8 (5.4-NR)		22.2 (4.2-100.0)	

Bold value indicates significant results ($P < .05$).

In conclusion, this study confirms the validity of the MALT-IPI in contemporary practice, but also delineates its limitations, particularly in patients with gastric EMZL managed with *H pylori* eradication or localized modalities. Integration of AD or ANA serostatus identifies a small subset of patients with dismal outcomes, but does not consistently improve prognostic accuracy across the broader cohort. These findings warrant further prospective validation and consideration in future trial designs, considering the potential limited prognostic power of the MALT-IPI in patients with primary gastric EMZL and upfront *H pylori* eradication treatment.

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Authorship

Contribution: V.S.-P. and M.R. conceived the conceptual idea and designed and performed the analysis; V.S.-P., B.K., I.S.-K., R.B., W.D., M.E.M., and M.R. contributed to data collection and interpretation of the results; V.S.-P. and M.R. wrote the manuscript; and B.K., I.S.-K., R.B., W.D., and M.E.M. critically reviewed the manuscript.

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ORCID profiles: V.S.-P., 0009-0006-9151-4139; B.K., 0000-0002-5490-2371; I.S.-K., 0000-0002-3814-7492; W.D., 0000-0002-7450-4215; M.E.M., 0000-0001-8786-8686; M.R., 0000-0002-3248-5802.

Correspondence: Markus Raderer, Division of Oncology, Department of Medicine I, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria; email: markus.raderer@meduniwien.ac.at.

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