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ORIGINAL ARTICLE

Validation of the Marginal Zone Lymphoma International Prognostic Index

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Abstract

The Marginal Zone Lymphoma International Prognostic Index (MALT-IPI) was recently developed for use in patients with mucosa-associated lymphoid tissue (MALT) lymphoma based on age, serum lactate dehydrogenase level, and Ann Arbor stage. In this study, we aimed to validate the MALT-IPI. A total of 455 MALT lymphoma patients were included in this study from between January 2005 and February 2017. Event-free survival (EFS), progression-free survival (PFS), cause-specific survival (CSS), and overall survival (OS) were the primary outcomes. Of the 455 patients, MALT-IPI low-, intermediate-, and high-risk groups included 309 (67.9%), 126 (27.7%), and 20 (4.4%) individuals, respectively. When comparing the low-risk group (L MALT-IPI) with the intermediate–high-risk group (I-H MALT-IPI), EFS, PFS, CSS, and OS were significantly different ($p = 0.000$, $p = 0.000$, $p = 0.027$, and $p = 0.037$). The International Prognostic Index and the Follicular Lymphoma International Prognostic Index failed to predict the prognosis of MALT lymphoma. Use of the MALT-IPI significantly differentiated L MALT-IPI from I-H MALT-IPI with respect to EFS, PFS, CSS, and OS. MALT-IPI is a valuable tool for the prediction of MALT lymphoma prognosis.

Keywords MALT-IPI · MALT lymphoma

Introduction

Marginal zone lymphomas (MZLs) are indolent B cell lymphomas that are characterized by the proliferation of B cells from the marginal zone of B cell follicles found in mucosa-associated lymphoid tissue (MALT), lymph nodes, and the spleen [1]. MZL is the fourth most common non-Hodgkin's lymphoma, accounting for 8.3 to 10% of all cases [2, 3]. MZLs can be divided into MALT lymphomas, nodal MZLs, and splenic MZLs due to their distinct clinical features, treatments, and prognoses [1, 4].

Though the International Prognostic Index (IPI) has been successfully used to stratify diffuse large B cell lymphomas, the use of the IPI for indolent lymphomas such as follicular lymphomas and mantle cell lymphomas has been questioned [5]. Consequently, new prognostic indices, including the Follicular Lymphoma IPI (FLIPI) and the Simplified Mantle-cell Lymphoma IPI, as well as various derivatives, have been developed [6–8]. Similarly, Thieblemont et al. recently introduced the MALT Lymphoma Prognostic Index (MALT-IPI) based on age, serum lactate dehydrogenase (LDH) level, and Ann Arbor stage. Age ≥ 70 years, elevated serum LDH, and Ann Arbor stages III or IV each represents notable factors of MALT-IPI, with patients with zero factors falling in a low-risk group (L MALT-IPI), those with one factor falling into an intermediate-risk group, and those with either two or three factors falling into a high-risk group [9]. To date, MALT-IPI has not been validated after the original publication, and differences could exist with regard to the use of it in another investigation. Thus, in the present study, we analyzed MALT lymphoma patients using the MALT-IPI to evaluate its usefulness and adaptability.

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Methods

Study design and data collection

This was a retrospective study that employed two prospective cohorts and one retrospective cohort (median follow-up 55 months) (Fig. 1). One prospective cohort (median follow-

up 63 months) included 129 MALT lymphoma patients who had been diagnosed between July 2008 and January 2012. The other prospective cohort (median follow-up 31 months) included 145 MALT lymphoma patients who had been diagnosed between February 2012 and February 2017. The single retrospective cohort (median follow-up 71 months) included 181 MALT lymphoma patients who had been diagnosed between January 2005 and February 2017. In total, 455 MALT lymphoma patients from these three cohorts were stratified into low-, intermediate-, and high-risk groups according to MALT-IPI score. They were also stratified according to IPI and FLIPI scores. We classified the spleen and tonsils as extranodal sites as was done by Thieblemont et al. Paired single organs were designated as stage 4.

For the purpose of this study, pathology was needed to diagnose MALT lymphoma, and the diagnosis was confirmed by pathology specialists. An important diagnostic feature of MALT lymphoma is the presence of lymphoepithelial lesions, defined by the infiltration and distortion of epithelial structures by aggregates of neoplastic lymphoid cells [10]. The immunohistochemistry results of the neoplastic cells of MALT lymphoma (e.g., CD20+, CD5-, CD10-, Bcl6-, and cyclin D1-) were used. Disease staging was confirmed through abdomen, chest, and neck computed tomography, 18F-fluorodeoxyglucose positron emission tomography–computed tomography, bone marrow biopsy, esophagogastroduodenoscopy, or colonoscopy, depending on the location of the disease.

The collected data were age; sex; disease stage; Eastern Cooperative Oncology Group performance status; extranodal involvement, nodal involvement, and bone marrow involvement; B symptoms (e.g., fever, night sweats); involved site; blood tests including hemoglobin, serum LDH, and β-2 microglobulin; treatment modalities including chemotherapy, radiotherapy, and surgery; and follow-up data including progression, discontinuation, death, and cause of death.

Statistical analysis

We stratified and analyzed the 455 MALT lymphoma patients, combining the two aforementioned prospective cohorts and one retrospective cohort, and validated the MALT-IPI [9]. Kaplan–Meier curves were used to measure event-free survival (EFS), progression-free survival (PFS), cause-specific survival (CSS), and overall survival (OS). EFS, PFS, CSS, and OS were defined as revised response criteria for malignant lymphoma in the present study as was also done by Thieblemont et al. [9, 11]. Differences between groups were analyzed using log-rank test. IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA) was used.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Among 620 patients with MZL who were identified by merging two prospective cohorts and one retrospective cohort of patients diagnosed in the specified time periods, 455 MALT lymphoma patients were analyzed (Fig. 1). One prospective cohort (median follow-up 63 months) included 148 MZL patients diagnosed between July 2008 and January 2012; of these, 129 were finally diagnosed with MALT lymphomas

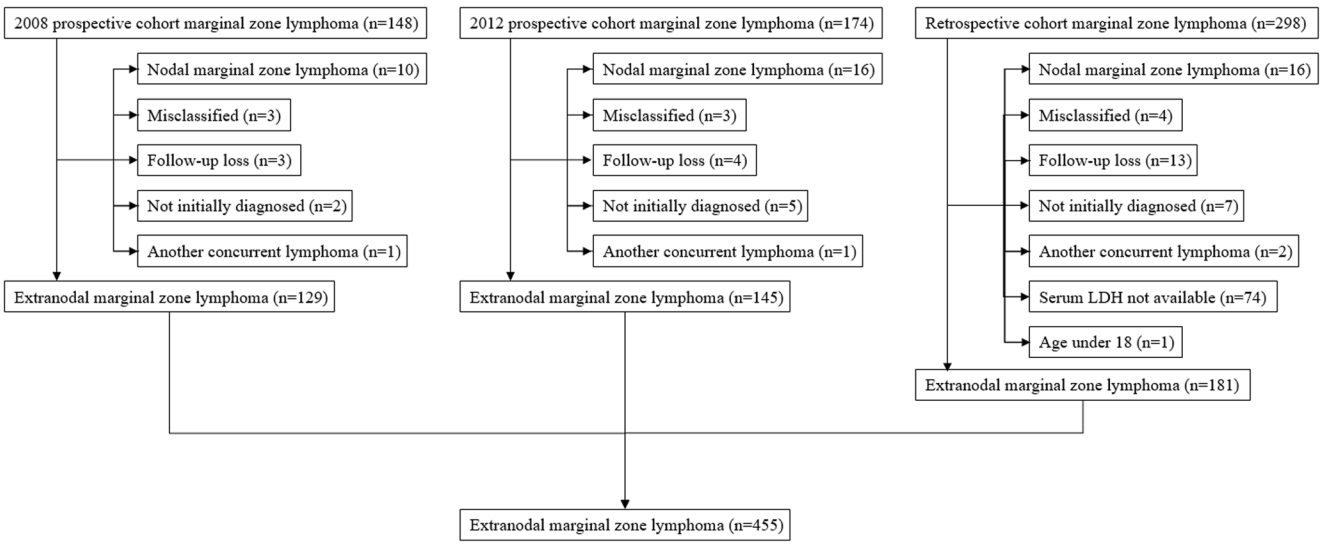

Fig. 1 Patient flow

and 10 with nodal MZL. Among the nine remaining patients, three patients were misclassified, three patients were lost to follow-up, one had both MALT lymphoma and lymphoplasmacytic lymphoma, and two patients were excluded because their enrollment time was not the first time the disease had been documented in their history. The other prospective cohort (median follow-up 31 months) included 174 MZL patients diagnosed between February 2012 and February 2017, with 145 of them finally diagnosed with MALT lymphomas and 16 of them diagnosed with nodal MZL. Among the 13 remaining individuals from this cohort, three patients were misclassified; four patients were lost to follow-up; one patient had both MALT lymphoma and diffuse large B cell lymphoma, which was dominant in the prognosis; and five referred patients whose baseline data were not able to be retrieved were excluded. The one retrospective cohort (median follow-up 71 months) included 298 MZL patients diagnosed between January 2005 and February 2017, broken down into 181 MALT lymphomas patients and 16 nodal MZL patients. Among the other 101 patients, serum LDH was not available for 74 patients, who demonstrated mostly stage 1 gastric MALT lymphomas. Additionally, there was one pediatric patient; 13 were lost to follow-up; two patients had other concomitant lymphomas, which were dominant in the prognosis; four patients were misclassified; and seven referred patients had baseline data that could not be retrieved.

The baseline characteristics of the final 455 MALT lymphoma patients are presented in Table 1. The median age at MALT lymphoma diagnosis was 52 years. Two hundred thirteen (46.8%) patients were male and 242 (53.2%) were female. Three hundred fifteen (69.2%) were stage 1, 43 (9.5%) were stage 2, four (0.9%) were stage 3, and 93 (20.4%) were stage 4. Of the included patients, 22 (4.8%) had elevated serum LDH levels (> 480 IU/L) and 433 (95.2%) had normal serum LDH levels. The median serum LDH level was 329 IU/L. Combining age, disease stage, and serum LDH level resulted in the MALT-IPI risk groups. Of the total study cohort, 309 (67.9%) had zero of three factors and were classified as the low-risk group, 126 (27.7%) had one of the three factors and were classified as the intermediate-risk group, and 20 (4.4%) had two or more of the three risk factors and were classified as the high-risk group.

For IPI risk group classification, 356 (78.2%) were in the low-risk group, 69 (15.2%) were in the low–intermediate-risk group, 25 (5.5%) were in the high–intermediate-risk group, and only five (1.1%) were in the high-risk group. Regarding performance status, 343 (75.4%) were 0, 105 (23.1%) were 1, and seven (1.5%) were 2, while there were no patients of performance statuses 3 or 4. Three hundred sixty-six (80.4%) patients had one extranodal involvement, while 89 (19.6%) had two or more extranodal involvements.

For FLIPI risk group classification, 382 (84%) were in the low-risk group, 58 (12.7%) were in the intermediate-risk

Table 1 Baseline characteristics of the 455 MALT lymphoma patients included in this study

	N	Percent
Median age (range), years	52.00 (18–88)	
Age ≥ 70 years	47	10.3
Sex		
Male	213	46.8
Female	242	53.2
Stage		
1–2	358	78.7
3–4	97	21.3
Elevated serum LDH (> 480 IU/L)	22	4.8
Performance status		
0–1	448	98.5
2–4	7	1.5
Extranodal involvement (> 1)	89	19.6
Nodal involvement (> 4)	9	2.0
Hb (< 12 g/dL)	76	16.7
Bone marrow involvement	18	4.0
Presence of B symptoms	33	7.3
Elevated β-2 microglobulin (> 2.4 mg/L)	59	15.6
Involved site		
Stomach	158	34.7
Orbit	149	32.7
Lung	44	9.7
Intestines	29	6.4
Skin	16	3.5
Spleen	11	2.4
Tonsil	10	2.2
Initial treatment modality		
Chemotherapy	83	18.2
Radiotherapy	201	44.2
Surgery	47	10.3
MALT-IPI		
Low risk	309	67.9
Intermediate risk	126	27.7
High risk	20	4.4
IPI		
Low	356	78.2
Low–intermediate	69	15.2
High–intermediate	25	5.5
High	5	1.1
FLIPI		
Low	382	84.0
Intermediate	58	12.7
High	15	3.3

LDH, lactate dehydrogenase; *Hb*, hemoglobin; *MALT-IPI*, Marginal Zone Lymphoma International Prognostic Index; *IPI*, International Prognostic Index; *FLIPI*, Follicular Lymphoma International Prognostic Index

group, and 15 (3.3%) were in the high-risk group. Four hundred forty-six (98%) had less than four nodal involvements and nine (2%) had more than five nodal involvements. Additionally, 76 (16.7%) had hemoglobin less than 12 g/dL and 379 (83.3%) had hemoglobin more than 12 g/dL.

Seventeen (3.7%) patients had bone marrow involvement and 438 (96.3%) had no bone marrow involvement. Thirty-three (7.3%) patients had B symptoms such as fever, weight loss, and night sweats, while 422 (92.7%) had no B symptoms. Among the 455 MALT lymphoma patients, 378 of them underwent the β-2 microglobulin test, with 59 (15.6%) having elevated β-2 microglobulin levels (> 2.4 mg/L). The mean β-2 microglobulin level was 1.66 mg/L.

The most commonly involved site of disease was the stomach: specifically, 158 (34.7%) had gastric MALT lymphoma. Additionally, 149 (32.7%) patients had MALT lymphoma involvement of the orbit; 44 (9.7%) had pulmonary MALT lymphoma; 29 (6.4%) had MALT lymphoma in the intestines, including the small intestine, colon, and rectum; 16 (3.5%) had skin MALT lymphoma; 11 (2.4%) had spleen involvement; and 10 patients had involvement of the tonsils.

Chemotherapy, radiotherapy, and surgery were predominantly used as initial treatment modalities. Eighty-three (18.2%) patients underwent chemotherapy, and most of the chemotherapy procedures included rituximab. Furthermore, 201 (44.2%) patients underwent radiotherapy, with most of them (87.1%) being treated using curative radiotherapy. Forty-seven (10.3%) patients underwent curative surgery including wedge resection or lobectomy of the lung, endoscopic mucosal resection or endoscopic submucosal dissection, polypectomy, cold biopsy, hemicolectomy, small bowel resection, parotidectomy, thymectomy, splenectomy, nephrectomy, orchiectomy, and skin resection.

EFS, PFS, CSS, and OS were not significantly different among the MALT-IPI risk groups in this study, even though poorer outcomes were expected with worse MALT-IPI scores. Estimated mean EFS values for the MALT-IPI low-, intermediate-, and high-risk groups were 131 months, 103 months, and 64 months, respectively. Estimated mean PFS values for the MALT-IPI low-, intermediate-, and high-risk groups were 135 months, 113 months, and 72 months, respectively. Estimated mean CSS values for the MALT-IPI low-, intermediate-, and high-risk groups were not obtained. Estimated OS values for the MALT-IPI low-, intermediate-, and high-risk groups were 146 months, 136 months, and 81 months, respectively.

Only 20 (4.4%) patients were included in the high-risk group in this study as compared with 68 (17%) in Thieblemont et al.'s study. So, we merged the intermediate- and high-risk groups into an intermediate–high-risk MALT-IPI (I-H MALT-IPI) group for further comparison. EFS, PFS, CSS, and OS were significantly different between the two groups of L MALT-IPI (67.9% of total study cohort) and I-H MALT-IPI (32.1% of total study cohort) (Fig. 2). The estimated mean EFS values for the L MALT-IPI and I-H MALT-IPI groups were 131 months and 102 months ($p = 0.000$), respectively. The estimated mean PFS values were 135 months and 113 months ($p = 0.000$), respectively. The estimated mean CSS values for L MALT-IPI and I-H MALT-IPI were not obtained ($p = 0.027$), while the estimated mean OS values were 146 months and 136 months ($p = 0.037$), respectively.

There was no uniform outcome finding in the gastric or nongastric MALT lymphoma subgroups. In the gastric

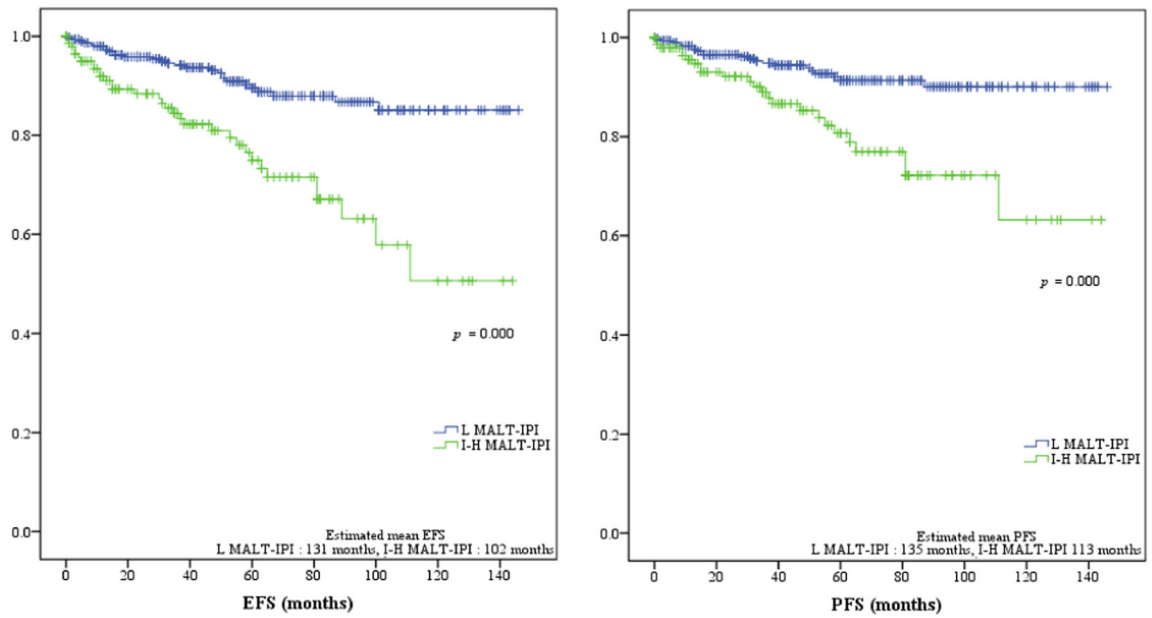

Fig. 2 Clinical outcomes according to MALT-IPI score achieved by comparing the L MALT-IPI and I-H MALT-IPI groups

MALT lymphoma subgroup, EFS and PFS were also significantly different between the L MALT-IPI and I-H MALT-IPI patients: specifically, the estimated mean EFS values were 129 months and 71 months, while the estimated mean PFS values were 133 months and 77 months, respectively. There was no specific cause of death in the gastric MALT lymphoma subgroup, and OS values were not significantly different. However, in the nongastric MALT lymphoma subgroup, EFS, PFS, and OS were significantly different between the L MALT-IPI and I-H MALT-IPI patients. Estimated mean EFS values were 131 months and 104 months for these groups, respectively. Additionally, estimated mean PFS values were 135 months and 115 months and estimated mean OS values were 147 months and 135 months, respectively. CSS values were not significantly different.

The use of IPI was not adequate to predict clinical outcomes in this study. IPI could not discriminate between the low-, low–intermediate-, high–intermediate-, and high-risk groups regarding clinical outcomes, EFS, PFS, CSS, and OS. However, when comparing the groups of low- and low–intermediate-risk with those of high–intermediate- and high-risk, EFS, CSS, and OS except PFS were significantly different (Fig. 3).

The FLIPI also failed to show predictability in patients with MALT lymphoma (Fig. 3). Considering the small number of patients in the intermediate- and high-risk groups, we combined these two groups and compared this new group with the

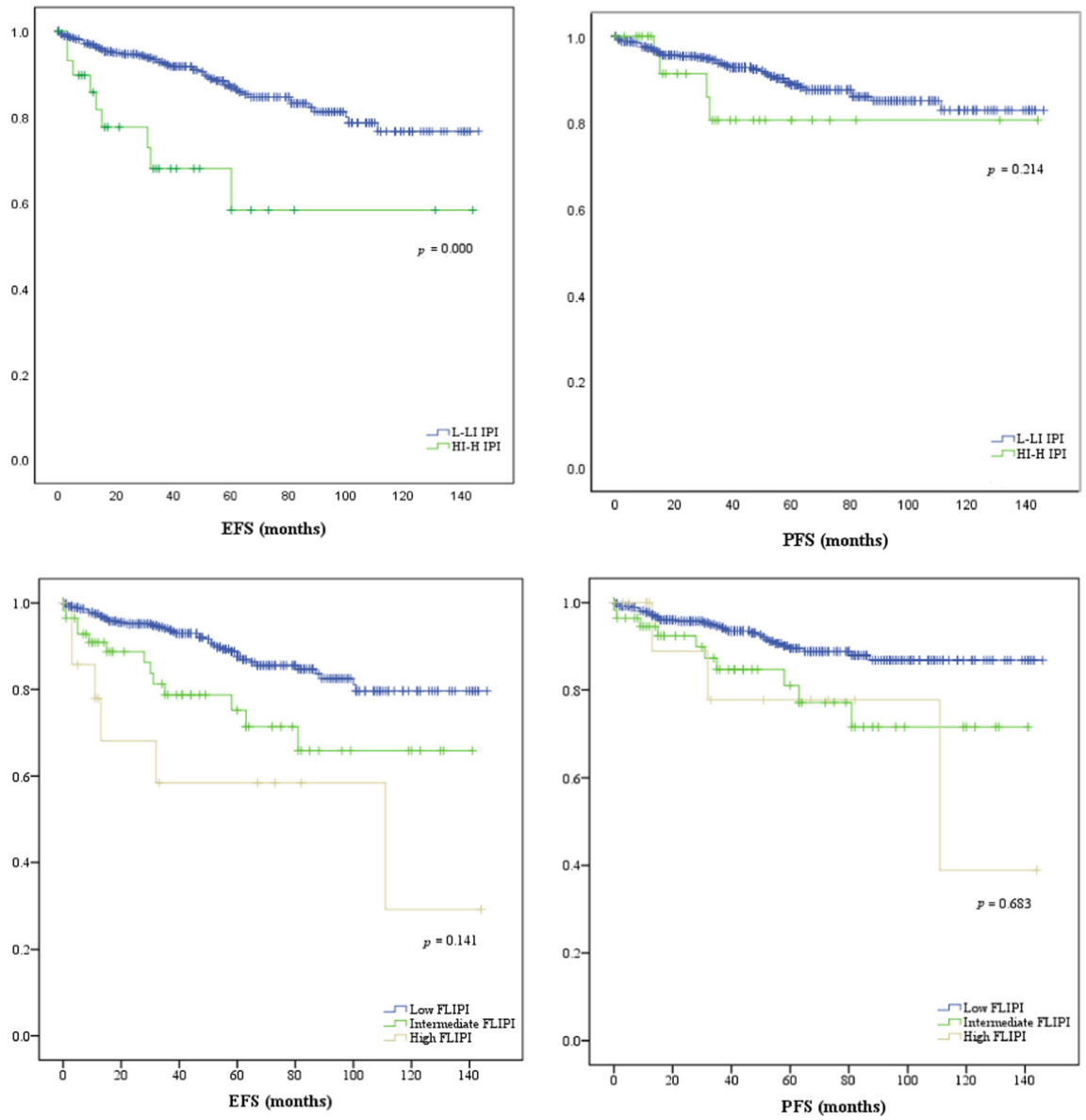

Fig. 3 Clinical outcomes according to the merged IPI (comparing the groups of low- and low–intermediate-risk with those of high–intermediate- and high-risk) and FLIPI groups

low-risk group. In this comparison, EFS, PFS, and CSS were significantly different, while OS showed a difference but not in a significant manner.

Discussion

To our knowledge, this is the first study to validate the newly developed MALT-IPI, other than the developers' own study. However, in this investigation, we failed to demonstrate MALT-IPI's discriminating ability. Because we only included a small number of MALT-IPI high-risk group patients, we merged the MALT-IPI intermediate- and high-risk groups into one group. Comparing the L MALT-IPI and I-H MALT-IPI groups showed a significant difference in EFS, PFS, CSS, and OS.

The small size of the MALT-IPI high-risk group might be due to our small number of elderly participants (10.3%), advanced-stage patients (21.3%), and patients with elevated serum LDH levels (4.8%). This dearth may be associated with Korea's unique circumstances, such as the easy accessibility to medical centers. The fact that staging was performed at the discretion of the clinicians might also contribute to the small size of the MALT-IPI high-risk group. However, almost all patients got full staging workups except a few patients. For example, if clinicians decided that a gastric MALT lymphoma patient has early-stage disease by esophagogastroduodenoscopy, abdomen pelvis computed tomography, and bone marrow biopsy, other examinations such as chest and neck computed tomography and 18F-fluorodeoxyglucose positron emission tomography–computed tomography might be excluded. In other words, this fact is unlikely to have influenced the result but this might introduce a small bias.

In the present study, there were only two cause-specific deaths. One case was of MALT-IPI intermediate risk and showed a histologic transformation to diffuse large B cell lymphoma combined with MALT lymphoma. For the purposes of our study, we counted this case as a cause-specific death, but the patient might have died from diffuse large B cell lymphoma. Another case was also MALT-IPI intermediate risk with bone marrow, spleen, and left paraaortic area involvement; this person died from disease progression with infection.

In our retrospective cohort, 74 patients' serum LDH levels were not available, and this population represents a large portion of our patients. Most of them were stage 1 gastric MALT lymphoma patients who were diagnosed early, around 2005 to 2006. At that time in our center, gastric MALT lymphoma patients routinely underwent esophagogastroduodenoscopy, abdomen pelvis computed tomography, bone marrow examination, and examination for Waldeyer's tonsillar ring involvement for staging, but not serum LDH level. After that point, however, gastric MALT lymphoma patients began to also undergo blood tests for serum LDH level. Also of note, the exclusion of these patients might contribute to the proportion of involved sites. Even though the stomach was identified as the most commonly involved site (34.7%), this might be incorrect. It is true that 43% of patients in Thieblemont et al.'s study were gastric MALT lymphoma patients [9], while other studies have shown 30 to 68% of MALT lymphoma patients having gastric MALT lymphoma [1, 4, 12, 13]. However, there was no significant difference in clinical outcomes between gastric and nongastric MALT lymphoma in Thieblemont et al.'s study, and this is controversial in several studies [4, 13, 14]. In other words, regarding the exclusion of patients whose serum LDH level data were unavailable, if this group was mainly composed of gastric MALT lymphoma patients, then this might not influence the validation of MALT-IPI in this study; in contrast, if these patients had other kinds of MALT lymphoma, then this is a potential issue.

Notably, even if this study failed to demonstrate the usability of MALT-IPI, there was a tendency for EFS, PFS, CSS, and OS to get worse relative to those for the MALT-IPI risk group. MALT-IPI high-risk group patients showed much poorer clinical outcomes than did low- and intermediate-risk group patients. MALT lymphoma is an indolent disease, responds well to treatment, and has a very favorable prognosis overall [15]. Considering this, dividing patients into three groups including a MALT-IPI high-risk group rather than two groups as we did will be much better if this prognostic index turns out to be useful in other MALT lymphoma groups. Further validation for the MALT-IPI needs to include a greater number of high-risk group patients. On the other hand, even if the MALT-IPI high-risk group showed much poorer clinical outcomes than did the MALT-IPI low- and intermediate-risk groups, the MALT-IPI high-risk group still did not show desperate clinical outcomes. EFS and PFS values were more than 5 years, CSS values were not obtained, and OS was 81 months in this study. Cause-specific deaths occurred in just two of the 455 patients included. Though not so with CSS and OS, EFS and PFS might represent more realistic clinical outcomes for MALT-IPI in following research efforts like the development of FLIPI 2 that sets PFS rather than OS as an endpoint [7].

Even comparing the L MALT-IPI and I-H MALT-IPI groups failed to show uniform clinical outcomes in the gastric and nongastric MALT lymphoma subgroups. In the gastric MALT lymphoma subgroup, only EFS and PFS were significantly different between the L MALT-IPI and I-H MALT-IPI patients. In the nongastric MALT lymphoma subgroup, EFS, PFS, and OS were significantly different between the L MALT-IPI and I-H MALT-IPI patients. This disagreement might be due to the small patient numbers or the need to establish realistic clinical outcomes.

Both the IPI and FLIPI were not adequate to use as predictive indices in MALT lymphoma in this study. Instead, they were available only in certain subgroups and in certain clinical outcomes. Similar results can be found in several studies [16–20]. These studies also failed to show the utility of the IPI and FLIPI in MZL or MALT lymphoma.

There are some limitations. Even though this study included two prospective cohorts and one retrospective cohort to achieve enrollment of more patients, there remained only a small number of MALT-IPI high-risk group patients available to validate the MALT-IPI, as previously noted. In addition, there were some missing information such as serum LDH level or follow-up data, especially in the retrospective cohort.

The use of the MALT-IPI did not discriminate between patients regarding clinical outcomes, EFS, PFS, CSS, and OS according to the MALT-IPI risk groups used in this study. However, in comparing the L MALT-IPI group with the I-H MALT-IPI group, EFS, PFS, CSS, and OS were found to be significantly different. Further validation research that includes more patients, especially in the MALT-IPI high-risk group, is warranted to confirm the usefulness of the MALT-IPI.

Compliance with ethical standards

This study was approved by the institutional review board (IRB) of Samsung Medical Center in Seoul, Korea (IRB number 2018-02-076).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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