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Research Article

# A Laboratory Prognostic Index Model for Predicting Survival in Patients with Malignant Pleural Mesothelioma

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## Abstract

**Objectives:** The prognostic significance of a Laboratory Prognostic Index (LPI) was demonstrated recently in non-small cell lung cancer (NSCLC). We investigated the predictive effect of LPI in patients with malignant pleural mesothelioma (MPM).

**Methods:** We retrospectively reviewed 68 patients with MPM in a single institution. LPI score was consist of serum levels of white blood cells (WBC≥10000/mm$^3$), lactate dehydrogenase (LDH≥248 U/L), albumin (≤3.5 g/dL), calcium (Ca≥10.5 mg/dL), and alkaline phosphatase (ALP≥120 U/L). Patients were classified into 3 LPI groups as follows: LPI0:normal; LPI1:with one abnormal laboratory finding; and LPI2:with at least 2 abnormal laboratory findings.

**Results:** The study included 53 patients with MPM. Median follow-up period was 11.4 (1-103) months. Median OS of all patients was 21.6 months (95% CI; 15.9–27.4). When patients were classified by LPI; median OS was 36.5 months (95%CI, 13.6-59.3) in patients with LPI0, 23.7 month s(95%CI, 19.8-27.6) with LPI1 and 11.5 months (95%CI, 5.5-17.6) with LPI2 (p=0.001). According to multivariate analysis higher LPI score at the time of diagnosis were independent poor prognostic variables for OS (p<0.05).

**Conclusion:** In this study, LPI was found to be a significant prognostic factor for OS in patients with MPM. LPI can be used as a non-invasive, easily applicable, practical prognostic factor in mesothelioma patients. We believe that this prognostic score meets the of unmet need on this subject in the literature.

**Keywords:** Laboratory Prognostic Index(LPI), malignant, mesothelioma, survival analysis.

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Malignant mesothelioma is a rare tumor, most commonly seen between 5th and 6th decades of life, with a poor prognosis.[1] Five-year survival rate is less than 10%. For malignant pleural mesothelioma (MPM), median overall survival time (OS) is 21 months for Stage I, decreasing to 12 months for Stage IV.[2] Females have a higher survival rate. Gender-related factors such as low exposure to asbestos and other environmental exposure, lower levels of smoking, early admission to the hospital and estrogen effect are emphasized.[3]

Histologic subtypes of mesothelioma include epithelioid, sarcomatoid and biphasic (mixed). Epithelioid subtype is the most common type with the better survival.[4]

A standardized treatment of mesothelioma has not been established yet. Lack of an ideal staging system, low success rate of R0 resection with surgery, inconsistent results for different subtypes due to different biological behavior of the disease, contradictory survival results of radiotherapy, patients often having advanced age and poor perfor-

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mance status are some of the causes why a standard therapy approach cannot be established yet.

A combined (tri-)modality (surgery, chemotherapy and radiotherapy) approach is often used in MPM patients with surgically resectable tumor in expert centers.

The only large head-to-head comparison of extrapleural pneumonectomy (EPP) versus pleurectomy/decortication (P/D) by experienced mesothelioma surgeons demonstrated better survival associated with PD than with EPP after controlling for histologic type, stage, multimodality treatment, and sex. Although arguments may be made because of the retrospective nature of this study, surgeon selection bias, and the variations in adjuvant treatment, the surgical numbers are sizeable for comparison. If we want to use EPP despite its higher operative risk, this would make sense if we saw huge differences in survival, but such differences are not observed. We actually see a worse survival with EPP than with PD. Practically, PD preserves more lung and demonstrates (at least) similar or better overall survival and decreased postoperative morbidity and mortality when compared with EPP, while patterns of recurrence remain local. The perceived oncologic benefits of EPP do not appear to translate into real benefits for the patient. Although superiority of P/D over EPP have not been definitely demonstrated, a better survival with P/D compared to EPP has been observed as P/D preserves more lung and has less postoperative morbidity and mortality.[5, 6]

It is more appropriate to leave the decion of surgical approach to the experience of the relevant center and surgeon. There are studies showing that surgical success of sarcomatoid and biphasic subtypes are lower, and some centers often do not recommended surgery in these subtypes.[7]

Systemic chemotherapy (CT) with pemetrexed plus a platinum compound (cisplatin or carboplatin) is the standard regimen for MPM. CT has been given both prior to surgery and as an adjuvant following surgery. Addition of bevacizumab to pemetrexed-cisplatin improved both PFS and OS compared with pemetrexed plus cisplatin in unresectable tumors.[8] The median survival of patients was extended from 18 months to 24 months with new treatment approaches. Major prognostic factors of survival in MPM are histologic subtypes, age, lymph node involvement and stage of disease.

Laboratory Prognostic Index (LPI) consists of a combination of leukocyte count, lactate dehydrogenase (LDH), albumin, calcium, alkaline phosphatase (ALP) levels which were previously reported as significant prognostic factors one by one, in various cancers. Components of LPI (leukocytosis, higher LDH levels, hypoalbuminemia, hypercalcemia, and higher ALP levels) reflect systemic inflammatory response and give clues about cancer development and progression. Leukocytosis and hypoalbuminemia are prognostic that reflect increased inflammatory response. In addition to being effective in tumor angiogenesis with its' hypoxic regulatory role, LDH is a peripheral indicator of tumor turnover with ALP. Hypercalcemia may be the peripheral reflection of paraneoplastic syndromes or an advanced stage tumor. Our aim is to investigate non-invasive and better predictor model for survival in daily practice.

## Methods

### Study Design and Patient Selection

We retrospectively reviewed medical records of patients with histologically confirmed MPM who were diagnosed and followed-up between February 2011 and July 2020 in a single institution. A total of 68 patients were retrieved and 15 extrapleural mesothelioma patients were excluded. Demographic and clinical characteristics of 53 patients were recorded. We used tumor-node-metastasis (TNM) staging according to AJCC cancer staging manual 8th Edition, 2017 for MPM.

Hematological and biochemical parameters including white blood cell (WBC) count, albumin, serum calcium, LDH, and ALP levels were also recorded, and LPI was calculated. The cut off values of the laboratory parameters validated in NSCLC trial was used in calculating LPI.[9] These cut off values were checked by roc analysis and accepted as appropriate values for our study. The cut off value for each parameter was defined as follows; leukocytosis: white blood cell ≥10.000/mL; hypoalbuminemia: serum albumin level ≤ 3.0 g/dL; ALP and LDH levels: above normal levels (≥120 U/L and ≥248 U/L respectively); hypercalcemia: serum calcium level ≥10.5 gr/dL. Using these parameters, we defined 3 LPI groups as follows: LPI 0: normal; LPI 1: one abnormal laboratory finding; and LPI 2: at least 2 abnormal laboratory findings.

Clinical and laboratory parameters analyzed together for predicting survival.

Updated cut-off date for survival was July, 2020.

Informed and written consent of patients who had participated the study was obtained.

### Statistical Analysis

All categorical variables were presented as frequencies and group percentages, ranges were denoted for parameters with a median value. Chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression models were conducted to assess factors that predicting survival.

Overall survival (OS) was defined as the time interval in months between the diagnosis of disease to death or last outpatient visit if the patient was still alive. OS was estimated with Kaplan-Meier method and log-rank test. Prognostic

factors for and OS were evaluated in univariate and multivariate Cox regression models. Age, gender and stage of disease were included in multivariate analyses regardless of their prognostic potentials. Statistical analyses were performed using SPSS 20.0 software. Confidence interval (CI) was selected as 95% and a 2-sided p value less than 0.05 was accepted as statistically significant.

## Results

### Patient Characteristics

A total of 53 patients with malignant pleural mesothelioma were included in the study, with a male predominance (56.6%) (Table 1). Median age at diagnosis was 59 (range: 39-83) years, and 29 (54.7%) patients were under 60 years.

**Table1.** Characteristics of the patients with LPI scores

| Descriptives | n(%)=53(100) | LPI0, n(%)=10(100) | LPI1, n(%)=26(100) | LPI2, n(%)=17(100) | p |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 30(56.6) | 6(60) | 15(57.6) | 9(52.9) | 0.92 |
| Female | 23(43.4) | 4(40) | 11(42.4) | 8(47.1) | |
| ECOG-PS | | | | | |
| ECOG 0 | 31(58.5) | 8(80) | 16(61.5) | 7(41.2) | 0.12 |
| ECOG 1-2 | 22(41.5) | 2(20) | 10(38.5) | 10(58.8) | |
| Diagnostic age | | | | | |
| <60 | 29(54.7) | 7(70) | 15(42.3) | 7(41.2) | 0.31 |
| ≥60 | 24(45.3) | 3(30) | 11(57.7) | 10(58.8) | |
| Smoking History | | | | | |
| Never smoker | 29(54.7) | 6(60) | 16(61.5) | 7(41.2) | 0.39 |
| Current/past smoker | 24(45.3) | 4(40) | 10(38.5) | 10(58.8) | |
| Asbestos exposure | | | | | |
| Yes | 6(11.3) | 0(0) | 4(15.3) | 2(11.8) | 0.42 |
| No | 47(88.7) | 10(100) | 22(84.7) | 15(88.2) | |
| Histopathology | | | | | |
| Epithelioid | 39(73.6) | 7(70) | 21(80.8) | 11(64.7) | 0.48 |
| Sarcomatoid and Biphasic | 14(26.4) | 3(30) | 5(19.2) | 6(35.3) | |
| Type of surgery | | | | | |
| EPP | 10(18.9) | 3(30) | 6(23.2) | 1(5.9) | 0.41 |
| PD | 25(47.2) | 5(50) | 12(46.1) | 8(47.1) | |
| Palliative surgery | 18(34) | 2(20) | 8(30.7) | 8(47.1) | |
| Pathological Stage | | | | | |
| Stage1 | 15(28.3) | 3(30) | 11(42.4) | 1(5.9) | 0.06 |
| Stage2 | 2(3.7) | 0(0) | 2(7.6) | 0(0) | |
| Stage3 | 18(34) | 5(50) | 5(19.2) | 8(47.1) | |
| Stage4 | 18(34) | 2(20) | 8(30.8) | 8(47.1) | |
| TNM staging for resected tumors | | | | | |
| T1 | 5(14.3) | 3(60) | 2(7.7) | 0(0) | 0.06 |
| T2 | 5(14.3) | 0(0) | 5(19.2) | 0(0) | |
| T3 | 17(48.6) | 3(17.6) | 8(30.8) | 6(35.3) | |
| T4 | 8(22.9) | 2(25) | 5(19.2) | 6(35.3) | |
| N0 | 21(66) | 5(23.8) | 13(50) | 3(17.6) | 0.07 |
| N1 | 11(31.4) | 1(9.1) | 5(19.3) | 7(41.2) | |
| N2 | 3(8.6) | 2(66.7) | 2(7.7) | 2(11.8) | |
| LVI for resected tumors | | | | | |
| Yes | 12(34.3) | 3(25) | 7(26.9) | 3(17.6) | 0.89 |
| No | 23(65.7) | 5(21.7) | 11(42.3) | 7(41.2) | |
| PNI for resected tumors | | | | | |
| Yes | 13(37.1) | 4(30.8) | 7(26.9) | 3(17.6) | 0.68 |
| No | 22(62.9) | 4(18.2) | 11(42.3) | 7(41.2) | |

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status. EPP: extrapleural pneumonectomy. P/D: pleurectomy/decortication. TNM: tumor-node-metastasis. LVI: Lymphovascular invasion. PNI: Perineural invasion. LPI: Laboratory Prognostic Index..

Thirty-one (58.5%) patients were Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) 0. Twenty-nine patients had a history of smoking, and 6 had a history of asbestosis exposure. When classified according to histological subtypes; 39 (73.6%) patients had epithelioid, 14 (26.4%) patients had sarcomatoid and biphasic histology. Eighteen (34%) patients were stage 4 at the time of diagnosis. Among operated 35 patients, 10 (18.9%) of them had EPP and 25 of them had P/D (47.2%), and only one patient refused adjuvant chemotherapy. Although seven patients received neoadjuvant chemotherapy, one was still inoperable. Five inoperable patients had never received chemotherapy during follow-up period. The most common first-line regimen was cisplatin plus pemetrexed (n=33, 62.3%). Thirty-nine (73.6%) patients received adjuvant or palliative radiotherapy during the treatment.

According to LPI scores 10 (18.9%) patients had LP 0, 26 (49.1%) patients had LPI 1 and 17 (32.1%) patients had LPI 3. Subgroup distrubitions of covarities were homogeneous (p>0.5).

## Survival Analysis

Median follow-up period was 11.4 (range:1-103) months in our clinic. Median age at diagnosis was 59 (range:39-83) years. Half of operated and 27 (77.1%) of 35 non-operated patients have relapsed at the time of final analysis. Median DFS was 13.7 months (95% CI; 7.7-19.8) for operated patients and median PFS was 7.6 months (95% CI; 5.4-7.8) for non-operated patients. Forty-two (79.2%) patients died during the follow-up, and median OS was 21.6 months (95% CI; 15.9–27.4). Median OS in patients with epithelioid histology was 24 months (95% CI; 19.7-28.4), and OS was 15 months (95% CI; 6.0-24) in sarcomatoid or biphasic histology (p=0.11).

Median OS in surgically resectable patients was 24.3 months (95% CI; 19.7-28.9) and in unresectable patients was 12.7 months (95% CI; 7.9-17.5) (p=0.049). According to method of surgery median OS was 23.7 months (95% CI; 12.8-34.6) in P/D and 26.7 months (95% CI; 21.8-31.6) (p=0.75) in EPP. The actual 1-, 2- and 3-year OS rates were 69%, 45%, and 22%, respectively.

## LPI Related Survival Analysis

LPI included white blood cell (WBC) count, albumin, serum calcium level, LDH, and ALP levels. Subgroups were classified as LPI 0: normal; LPI 1: one abnormal laboratory finding; and LPI 2: at least 2 abnormal laboratory findings.

Ten (19%) patients had LPI 0, 26 (49%) patients had LPI1 and 17 (32%) patients had LPI2 in the study.

Median OS was 36.5 months (95%CI, 13.6-59.3) in patients with LPI0, 23.7 months (95%CI, 19.8-27.6) with LPI1 and 11.5 months (95%CI, 5.5-17.6) with LPI2 (p=0.001). For patients with LPI 0, 1 and 2, 1-year survival rates were 100%, 73% and 45%; 2-year survival rates were 78%, 41% and 19%, respectively. 3-year survival rates were 62%, 21% and 4%, respectively.

Survival analysis according to parameters that composed LPI is given in Table 2, and Kaplan-Meier survival curves for OS according to LPI is given in Figure 1.

**Table 2.** Survival Analysis According to LPI parameters

| | n(%) | OS(months) (CI%) | p |
|---|---|---|---|
| LDH groups | | | |
| ≤248 U/L | 34(64.2) | 24.3(14.5-34.0) | 0.006 |
| >248 U/L | 19(35.8) | 16.5(3.0-30.0) | |
| Albumin groups | | | |
| ≥3 g/dL | 37(69.8) | 24.3(19.1-29.4) | 0.014 |
| <3 g/dL | 16(30.2) | 11.7(10.4-13.1) | |
| WBC groups | | | |
| ≤10000 / mL | 37(69.8) | 24.3(20.4-28.1) | 0.005 |
| >10000 / mL | 16(30.2) | 11.5(3.7-19.4) | |
| ALP groups | | | |
| ≤120 U/L | 35(66) | 23.7(18.1-29.3) | 0.86 |
| >120 U/L | 18(34) | 15.0(5.4-24.6) | |
| Ca groups | | | |
| ≤10.5 gr/dL | 52(98.1) | 21.7(16.0-27.4) | 0.49 |
| >10.5 gr/dL | 1(1.9) | 13.7(not calculated) | |
| LPI groups | | | |
| LPI 0 | 10(18.9) | 36.5(13.6-59.3) | 0.001 |
| LPI 1 | 26(49.1) | 23.7(19.8-27.6) | |
| LPI 2 | 17(32.1) | 11.5(5.5-17.6) | |

OS: Overall survival; LDH: lactate dehydrogenase; WBC: white blood cells; ALP: alkaline phosphatase; Ca: calcium; LPI: Laboratory Prognostic Index.

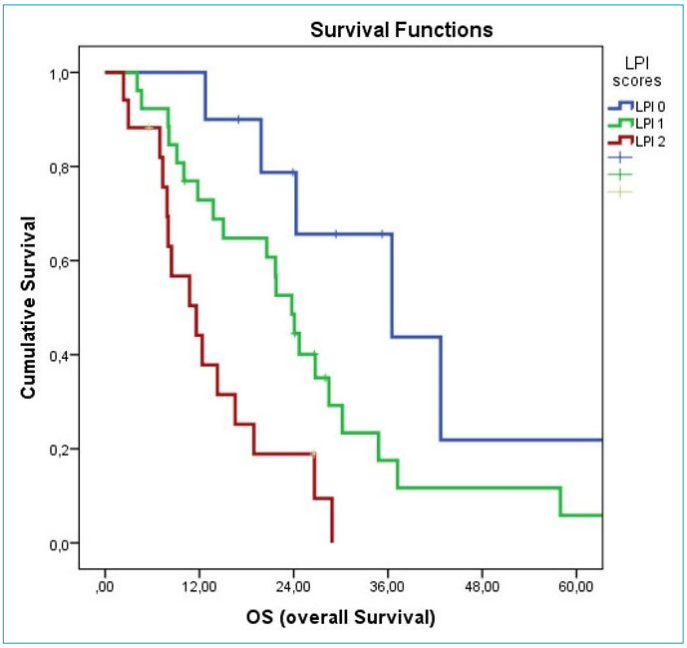


**Figure 1.** Kaplan-Meier Survival Curve for Overall Survival According to LPI.

### Univariate and Multivariate Analysis

Age, ECOG-PS, history of surgery, histological diagnosis, stage of disease, LPI groups were significant prognostic variables for OS in univariate analysis (p<0.05). Older age, non-epithelioid histology and higher LPI score at the time of diagnosis were independent poor prognostic factors for OS in multivariate analysis (p<0.05) (Table 3).

## Discussion

In our study we investigated the predictive value of LPI model which was demonstrated in NSCLC before. In mesothelioma, variable biology and behavioral patterns as well as guiding prognostic markers are important due to lack of a standardized treatment approach. There is a strong need for non-invasive prognostic indicators that can be used in daily practice.

Prognostic models have been the focus of research in MPM because of its' aggressive future and have no standard treatment approach and ideal staging system.

Several prognostic models have been developed for MPM before, including pathologic and laboratory parameters. The European Organisation for Research and Treatment of Cancer (EORTC) scoring,[10] the Cancer and Leukemia Group B (CALBG) index,[11] Glasgow Prognostic Score (mGPS)[12] have been previously reported in the literature as scores predicting survival. Unfortunately, none of these models is considered ideal.

As inflammatory response plays a key role in the pathogenesis of MPM, we investigated the prognostic value of inflammation-based LPI score for predicting overall survival. LPI is a model based on WBC count, albumin, serum calcium level, LDH and ALP levels. We explained below some studies showing the effect of each parameter on cancer survival. LPI was validated as a prognostic model in patients with advanced NSCLC.[9] There is no data of the impact of LPI on survival for MPM.

Systemic inflammatory response that can be demonstrated from peripheral blood is very important for tumor microenvironment, cancer development and progression. Evidence has also shown that increased systemic inflammation was associated with poor OS in various types of cancer.[13, 14] Neutrophils,[15] platelets,[16] and lymphocytes[17] have been reported as inflammation related cells in recent studies. In previous studies, leukocytosis has been reported as a poor prognostic factor for MPM.[10] In our study leukocytosis was also associated with shorter survival (p=0.005).

Unlike normal cells, cancer cells tend to employ alternate metabolic pathways.[18] They generate adenosine triphosphate (ATP) mainly through anaerobic glycolysis. LDH as a hypoxia-regulator plays a vital role in anaerobic glycolysis.[19] LDH, which is related to intratumoral hypoxia, increases macrophage mediated angiogenesis and invasion ability.[20] An increased LDH level was shown to be associated with resistance to chemotherapy and radiation therapy.[21] Prognostic value of serum LDH has been demonstrated in several tumors, including NSCLC, colorectal cancer, prostate cancer as well as other solid tumors.[22-24] As determined in our study, several studies have assessed the prognostic value of elevated pretreatment LDH levels

**Table 3.** Univariate and multivariate analysis that predicting overall survival

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p | HR (95% CI) | p |
| Gender (Female vs. male) | 1.5 (0.80-2.80) | 0.19 | 1.89(0.95-3.75) | 0.67 |
| ECOG-PS (≥1 vs. 0) | 3.1 (1.50-6.05) | 0.001 | 1.74(0.74-3.90) | 0.17 |
| Age (≥60 vs. <60) | 2.00 (1.04-3.87) | 0.03 | 2.34(1.16-4.69) | 0.016 |
| Smoking (current/past smoker vs. never smoker) | 1.13 (0.61-2.10) | 0.68 | | |
| Asbestosis exposure (yes vs. no) | 1.17 (0.51-2.67) | 0.70 | | |
| Histopathology (non-epithelioid vs. epithelioid) | 1.71(0.86-3.40) | 0.04 | 2.25(1.08-4.68) | 0.03 |
| Underwent surgery (no vs. yes) | 1.87(0.93-3.19) | 0.04 | 1.07(0.47-2.42) | 0.16 |
| Irradiation to thorax (yes vs. no) | 1.44(0.69-3.02) | 0.32 | | |
| Pathological Stage (4 vs.others ) | 1.86 (0.96-4.57) | 0.06 | 1.33(0.63-2.77) | 0.44 |
| Applied adjuvant or neoadjuvant CT (no vs yes) | 1.11(0.46-2.67) | 0.81 | | |
| LPI gruops | | | | |
| LPI ≥1 vs <1 | 2.68(1.11-6.44) | 0.02 | 3.22(1.25-8.28) | 0.015 |
| LPI1 vs. LPI0 | 2.08(0.83-5.20) | 0.11 | | |
| LPI2 vs LPI1 | 5.66(2.06-15.48) | 0.001 | | |

HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern Cooperative Oncology Group-Performance Status. CT: chemotherapy. LPI: Laboratory Prognostic Index.

for the prediction of survival outcomes in malign mesothelioma.[25, 26]

Malnutrition and inflammation suppress albumin synthesis. As a result, serum albumin is generally used to assess the nutritional status, severity of disease, disease progression and prognosis. Serum albumin has also been described as an independent prognosticator of survival in various cancers. It has also associated with decreased treatment response and increased risk of chemotherapy induced toxicity. Hypoalbuminemia has been included in many scoring systems showing cancer related survival.[27-29] In our study, patients presenting with hypoalbuminemia had shorter survival (p=0.014).

Although ALP is mostly associated with high bone turnover and metastasis, its major function is transporting across cell membranes. There are ALP isoenzymes that have been shown to correlate with cancer improvement in experimental studies. Patients with higher ALP levels had a trend of lower survival in our study.

Malignancy associated hypercalcemia at the time of diagnosis was found to be associated with poor prognosis, and normalization of hypercalcemia other than antitumoral therapy did not improve survival. In cancer patients, many mechanisms play a role in hypercalcemia development and can be seen either as a paraneoplastic syndrome or as a result of bone metastases.[30] The most common mechanism is the secretion of a parathyroid hormone-related peptide by tumor cells . In our study, we could not comment on the effect of hypercalcemia on survival alone as there was only one patient with hypercalcemia at the time of diagnosis.

## Conclusion

In conclusion, our aim was to provide a cheap, easily accessible, and reproducible prognostic index which can differentiate patients who are going to live longer with trimodality therapy for MPM. We demonstrated that LPI is an independent prognostic factor for MPM as shown in NSCLC. As we explain in the text, LPI score is a powerful score because of combination these valuable parameters.

We believe that clinical trials to rule out the impact of consecutive LPIs in tailoring treatment, and using more aggressive or new treatment approaches for patients with a high LPI score, could be planned. Also more comprehensive and prospective studies can be performed to improve the statistical significance of our findings. The relationship between pathology or genetic profile and LPI score can be evaluated.

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### Disclosures

**Ethics Committee Approval:** All procedures performed were in accordance with ethical standards of institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study has been approved by Marmara University Ethical Committee with a number of 09.2019.1014.

**Peer-review:** Externally peer-reviewed.

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**Authorship Contributions:** Concept – T.B.; Design – T.B..; Supervision – F.Y.; Materials – T.B., N.C.D.; Data collection &/or processing – M.C., T.K.G., M.U.C., R.A., N.C.D., T.A.T.; Analysis and/or interpretation – T.B., O.E.; Literature search – T.B.; Writing – T.B.; Critical review – P.F.Y., F.D.

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