Risk Stratification in Differentiated Thyroid Cancer with RAI-avid Lung Metastases

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Abstract

Objective: Radioactive iodine (RAI) therapy is effective for differentiated thyroid cancer (DTC) patients with lung metastasis. However, some patients have poor prognosis despite the RAI accumulation. The utility of inflammatory biomarkers, including neutrophil-to-lymphocyte ratio (NLR), has been reported as a prognostic factor for many carcinomas. This study aimed to investigate the risk factors related to DTC patient survival with RAI-avid lung metastasis and to attempt risk stratification.

Design and methods: This retrospective study included 123 patients with RAI-accumulating lung metastatic DTC. The cause-specific survival (CSS) rate from the time of detection of lung metastasis was tested using the Kaplan–Meier log-rank test, and the multivariate analysis was calculated using the Cox proportional hazards model. NLR was retrospectively calculated using the blood sample collected before initial RAI treatment. The NLR cutoff value was 2.6 on the ROC curve.

Results: Age ≥55 years at time of operative treatment, follicular carcinoma, lung metastasis tumor ≥10 mm in diameter, age ≥55 years at the time of detection of lung metastasis, age ≥55 years at the time of RAI treatment, and NLR ≥2.6 at the initial RAI treatment were predictive of decreased CSS. Multivariate analysis identified that the independent prognostic factors were lung metastatic tumor ≥10 mm in diameter and NLR ≥2.6. Patients in the high-risk group with both factors had significantly lower CSS rates than those in the low- and intermediate-risk groups with one or none of these factors.

Conclusions: The high-risk group patients had significantly poorer survival, and these patients could be considered as future candidates for tyrosine kinase inhibitor therapy.
Introduction

The incidence of thyroid cancer has increased over the previous decade. The 5- and 10-year relative survival rates for patients with differentiated thyroid cancer (DTC) are 90%–95% \(^1\) \(^2\). Distant metastasis occurs in 5%–20% of patients with DTC and is predominantly observed in the lungs and bone \(^3\)\(^-\)\(^6\). When treating metastatic tumors of differentiated thyroid carcinoma, favorable prognosis can be expected after radioactive iodine (RAI) therapy after total thyroidectomy \(^7\). Therefore, RAI therapy is effective for patients with DTC with metastasis; only two-thirds of distant metastases has been reported to show substantial RAI uptake, and only approximately 42% cases are cured \(^8\). Moreover, RAI therapy is ineffective in approximately 30% of cases of DTC with distant metastasis \(^8\)\(^,\)\(^9\).

In recent years, cases in which disease progresses after RAI therapy or accumulation does not occur are considered cases of RAI-refractory differentiated thyroid cancer (RAIR-DTC), for which treatment with tyrosine kinase inhibitors (TKI) is to be considered. The 10-year survival rate of patients undergoing RAIR-DTC is reported to be <10% and prognosis is poor \(^8\), \(^10\). The criteria to determine RAIR are as follows: 1) no accumulation of RAI, 2) tumor growth even with little accumulation of RAI, and 3) tumor growth after RAI therapy (≥600 mCi). Based on the American Thyroid Association Guidelines, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT), whole-body scan (WBS), CT, and serum thyroglobulin (Tg) are recommended in combination for identifying RAIR-DTC \(^7\), but none of these tests are simple or convenient. In principle, patients with metastatic disease showing RAI accumulation should continue with RAI therapy, but whether it is refractory needs to be determined after several RAI treatments, and no studies have yet suggested any clinical features to help make a decision in the early stages of RAI therapy. Some recent reports indicate the efficacy of improving prognosis via TKI treatment in RAIR cases \(^10\), \(^11\). Ideally, in the case of continued RAI therapy, the likelihood of resistance to RAI therapy should be determined at the appropriate time, and more time should be spent on effective treatments, including TKI.
administration. Hence, searching for predictable biomarkers that may contribute to the selection of appropriate treatment methods is necessary.

Systemic inflammatory biological reaction is associated with cancer cell proliferation and worsened prognosis. Neutrophil-to-lymphocyte ratio (NLR), one of the indicators of inflammation and immunology, is easily measured via peripheral blood sampling and is reportedly useful as a prognosis index of various types of cancer. Several studies have investigated the role of NLR in thyroid cancer, and reports evaluating changes in inflammatory markers and blood-cell count due to RAI treatment exist, but no reports of studies on the correlation between NLR and prognosis in patients with RAI-avid lung metastasis were found. This study aimed to determine the clinical prognostic factors, including NLR, in RAI-avid lung metastasis cases and to attempt risk classification to identify future cases for TKI therapy.

**Patients and Methods**

This was a retrospective study of patients diagnosed with DTC at our hospital. RAI treatment was performed in 481 patients with distant metastasis of DTC at Ito Hospital from January 2000 to December 2018. A total of 387 (80.5%) patients showed metastatic lung tumors at the first time of metastatic lesion diagnosis, of which 129 (33.3%) displayed RAI accumulation at the time of first RAI treatment. Of the 129 patients who showed accumulation in the lungs, six patients were excluded from the study because they only underwent a WBS with a small amount of iodine to confirm accumulation and a therapeutic dose was not administered. Among the patients of DTC with lung metastasis treated using RAI, we retrospectively reviewed 123 cases with accumulation in metastatic lesions (Fig.1). The only organ that demonstrated metastasis at the time of the first RAI treatment was the lung. Furthermore, nine cases of bone metastasis and three cases of multi-organ metastasis were observed during follow-up. No cases with infection or inflammatory disease were noted at the time of metastatic lesion diagnosis. Lung metastasis was confirmed by any of the following methods: 1) lung metastatic lesion pathologically
confirmed by biopsy specimen, 2) localized or diffused uptake into the lungs confirmed by WBS, and 3) metastasis indicated by diagnostic imaging, such as chest CT. Metastases diagnosed within 6 months after initial operative treatment were considered as synchronistic lung metastases cases.

All patients in this study underwent total thyroidectomy. Prophylactic central lymph node dissection was routinely performed when the patients underwent thyroidectomy. Lateral lymph node dissection was performed in the presence of CT, ultrasound, or clinically evident lymph node involvement using a compartment-based approach. RAI dose per treatment was 3.7 GBq (100 mCi). A post-therapy WBS was performed 2 days after iodine-131 administration. RAI accumulation was determined using whole-body scintigraphy. Treatment was performed approximately every year while monitoring the intensity of RAI accumulation, Tg (thyroglobulin) levels under TSH stimulation, and the status of lung masses using CT. Peripheral blood was collected on the day of initial RAI treatment. Lung metastases were evaluated using CT. After treatment, TSH suppression therapy was performed via oral administration of levothyroxine sodium with target serum TSH of <0.1 μIU/mL.

The endpoint of this study was cause-specific survival rate (CSS), and the evaluation items were age at initial operation, sex, histopathology, time of lung metastasis detection, and maximum tumor diameter at time of lung metastasis detection, age at initial RAI treatment, and NLR at time of initial RAI treatment. NLR was calculated by dividing the peripheral blood neutrophil count immediately before the first RAI treatment by the peripheral blood lymphocyte count. A receiver operating characteristic (ROC) curve was used to determine the cutoff value of NLR at initial RAI treatment in predicting prognosis. Furthermore, prognosis was analyzed by stratification on the basis of the presence or absence of extracted independent prognostic factors.

Statistical Analysis
Differences in medians between the groups were compared with nonparametric Kruskal–Wallis tests. The CSS rate was calculated using the Kaplan–Meier procedure starting from the time when distant metastasis was detected, and a log-rank test was used to determine the significance. The Cox proportional hazards model was performed to determine the hazard ratio (HRs) of variables with 95% confidence intervals (CIs) for survival rate. Multivariate analysis using the Cox proportional hazards model was conducted for parameters shown to be significant in the univariate analysis. Statistical analysis software JMP (version 12; SAS Institute Inc., Cary, NC) was used for statistical analyses and a p-value of <0.05 was considered statistically significant for all tests. All patients were verbally informed about the study at the time of treatment, which was approved by the institutional review board of Ito Hospital.

**Results**

**Patient characteristics**

Patient characteristics are shown in Table 1. Median patient age at the time of initial surgery is 41 (range: 4–77) years. The male: female ratio was 1:2.7, and histological type was papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) in 83 (67.5%) and 40 (32.5%) patients, respectively. Median age at discovery of lung metastasis was 47 (range: 6–78) years; 67 (54.5%) and 56 (45.5%) patients had synchronous and metachronous lung metastasis, respectively. The median lung tumor diameter during initial RAI treatment was 7.5 (range: 1–40) mm. The median time to detection of distant metastasis in case of metachronous detection was 90 (range: 8–329) months. The median age at the time of initial RAI treatment was 48 (range: 7–78) years, the total RAI dose (median) was 258 mCi, and the total RAI dose exceeded 600 mCi in 10 patients. Median NLR at initial RAI treatment was 1.79. The median follow-up period with July 2020 as the final observation date was 147 (14–534) months. The cumulative CSS rates in all patients were as follows: 5 years, 91.6%; 10 years, 90.3%; and 15 years, 81.1% (Fig. 2).
The optimal NLR cutoff value was calculated by drawing an ROC curve. As a result, the NLR cutoff value before the initial RAI treatment was 2.615, sensitivity was 0.5714, specificity was 0.8378, and the area under the curve was 0.6966 (Fig. 3A). All patients were divided into groups with NLR of <2.6 or NLR of ≥2.6, and the CSS rates were compared. A significant difference in survival was observed between the two groups, and the cause-specific cumulative survival in the NLR ≥2.6 group was as follows: 5 years, 79.5%; 10 years, 73.3%; and 15 years, 55.0% (p = 0.0003) (Fig. 3B).

Analysis of prognostic factors (Table 2)

The results of univariate analysis using the Cox proportional hazards model revealed the following prognostic factors: age ≥55 years at time of operative treatment (p < 0.0001), follicular carcinoma (p = 0.0123), lung metastasis tumor ≥10 mm in diameter (p = 0.0006), age ≥55 years (p < 0.0001) at the time of detection of lung metastasis, age ≥55 years (p < 0.0001) at the time of RAI treatment, and NLR ≥2.6 at the initial RAI treatment (p = 0.0003). In multivariate analysis, lung metastatic tumor ≥10 mm in diameter (hazard ratio [HR]: 5.93; 95% confidence interval [CI]: 1.402–44.980; p = 0.0129) and NLR ≥2.6 at the initial RAI treatment (HR: 7.41; 95% CI: 2.229–29.438; p = 0.0011) were used as independent prognostic factors.

Stratified analysis of prognostic factors for CSS

The two extracted prognostic factors, i.e., lung metastatic tumor ≥10 mm in diameter and NLR ≥2.6 at the initial RAI treatment, were stratified using the number of corresponding factors. Prognosis was analyzed based on stratification of the group with 0 items as the low-risk group, the group with 1 item as the intermediate-risk group, and the group with all 2 items as the high-risk group. Patient characteristics based on risk stratification are shown in Table 3. Patients
with higher risk were significantly more likely to have older age at surgery, follicular carcinoma, older age at distant metastases detection, larger metastatic lung tumor diameter, older age at start of RAI treatment, and higher NLR. As depicted in Figure 4, the 5-year, 10-year, and 15-year survival rates after metastasis detection in the high-risk group were 69.5%, 59.7%, and 19.9%, respectively, which were much worse than those in the low- and intermediate-risk groups (Table 4). The prognosis was good in the low-risk and intermediate-risk groups, but poor in the high-risk group.

Discussion

Distant metastasis of DTC is not uncommon during treatment, which may be either diagnosed at the time of thyroid cancer detection or during follow-up \(^{18,19}\). In PTC and FTC with distant metastasis, RAI treatment is the first choice unless the patient loses RAI accumulation capacity \(^{20}\). Patients with distant metastases can have a long-term survival depending on the extent of radioiodine uptake in the distant metastases. The fact that iodine activity in metastases is a statistically significant favorable prognostic factor has also been confirmed by other investigators \(^{21-23}\). Even in those patients who accumulate iodine in distant metastases, there are cases that resist treatment and continue to progress. Such radioiodine-resistant patients are candidates for TKI therapy. In this study, we hypothesized that by identifying predictable prognostic factors at the initial stage of RAI treatment in patients with DTC and RAI-avid lung metastases, we could consider the appropriate time for treatment selection. As a result, we found that NLR \(\geq 2.6\) at the time of the first RAI treatment and maximum lung metastasis diameter \(\geq 10\) mm at the time of RAI treatment were poor prognostic factors. In addition, the presence of both these factors was also a poor prognostic factor.

RAI therapy forms the core treatment of DTC with distant metastasis. Durante et al. examined 441 patients with distant metastasis of DTC and reported that factors of poor prognosis include male sex, age \(\geq 40\) years, poor differentiation, and no accumulation of iodine \(^{8}\).
Nixon et al. reported that prognosis was determined based on the presence of nonlung metastatic lesions, including bone metastasis, and the absence of RAI accumulation. The presence or absence of RAI accumulation, size of metastatic lung tumor, histopathological type, and the timing of appearance of metastasis has been reported to affect prognosis. Therefore, the efficacy of treatment may depend on the ability of metastatic lesions to iodine uptake.

Song et al. reported that among patients with lung metastases from DTC, including those with RAI accumulation in lung metastases, poorer prognosis was seen in patients with lung metastatic tumor diameter of $\geq 1$ cm, age $\geq 40$ years, and metastases in organs other than the lung. In this study, lung metastasis with tumor diameter of $\geq 1$ cm was an independent prognostic factor.

In clinical practice, as long as there is RAI accumulation in the metastatic lesion under RAI therapy, RAI is continued if the disease does not progress or treatment is successful. However, the disease may progress during the course of treatment, and in recent years, molecular-targeted drug therapeutic agents, such as TKIs, have been broadly introduced to treat distant metastases of differentiated cancers in patients with thyroid cancer showing RAI resistance. When performing RAI therapy, data for determining whether there is constant resistance to treatment are indispensable, and determining the prognosis at an early stage is important.

NLR has been reported as a prognostic factor for various carcinomas, suggesting that high NLR level and prognosis might be related. An increased neutrophil count promotes tumor growth and metastasis due to the fact that neutrophils play an important role in the production of ligands that induce tumor cell proliferation and infiltration and cytokines that induce angiogenesis. Moreover, lymphocytes control the host’s immune function, and lymphocyte depletion impairs the host’s antitumor immunity, leading to worsened prognosis. Hence, NLR is regarded to reflect the balance between the tumor-promoting environment and antitumor immune status.

To date, several reports concerning NLR, prognosis, and recurrence exist, especially...
Regarding papillary thyroid cancer. Kim et al. reported that a high NLR is a prognosis predictor for disease-free survival (DFS) in patients with stage III or IV papillary thyroid cancer. Lee et al. reported that preoperative NLR for papillary thyroid cancer in patients aged ≥45 years is an independent predictor of DFS. In a meta-analysis of 3,081 patients, Feng et al. reported that pretreatment NLR may be an excellent biomarker for predicting tumor size, metastasis, and prognosis in thyroid cancer. In this study, NLR levels at the time of initial RAI treatment was confirmed to be a useful biomarker correlated with prognosis in patients with RAI-avid lung metastasis. It was possible to explore the prognostic indicators by stratification based on risk factors. If a patient has both a lung mass ≥1 cm and a high NLR, the prognosis is very poor.

Demir et al. examined the changes in inflammatory markers after RAI treatment in patients with DTC over time using RAI treatment, non-RAI treatment, and healthy subject groups; NLR was found to increase significantly 2 months after RAI. Although NLR subsequently and comparatively decreased, it remained high, and this change was reportedly due to systemic inflammation caused by RAI ablation to residual thyroid tissue. Furthermore, Kutlutuk et al. observed blood-cell count variability due to thyroid hormone fluctuations in patients during RAI treatment, and reported no statistical difference due to thyroid hormone fluctuations. In this study, the NLR measurement time of the patients was uniform immediately before RAI treatment in the environment of elevated thyroid-stimulating hormone, and considering the effects of RAI treatment was not necessary.

In general, there are no clear criteria for the cutoff value of NLR. Malnutrition and poor immunity can also increase the NLR. However, RAI treatment is not applied for patients with poor general health. Therefore, the NLR values in this study were considered to reflect the influence of tumor-related factors. When using these indicators, it is important to always re-evaluate the interpretation of the numerical values, giving due consideration to the purpose of use, the characteristics of the target population, the stage of the disease, etc.

This study has several limitations. It was a retrospective study and included patients who had
undergone RAI treatments ranging from 1 to 8 and included those who initially showed RAI uptake but lost the uptake after repeated treatments (RAI-resistant patients). In addition, cases in which other organ metastases, such as bone metastases, appeared during the follow-up were not excluded, which might have affected the prognosis.

Conclusion

Among cases of lung metastases of differentiated thyroid carcinoma with RAI accumulation, those with high NLR at initial RAI treatment and those with lung metastasis tumor ≥10 mm in diameter may have a poor prognosis. As a result of risk stratification based on prognostic factors, the prognosis of the high-risk group was found to be extremely poor, which means that they can be considered as candidates for TKI therapy in the future.

Declaration of interest

The authors declare no conflict of interest in this work.

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Figure legends

Figure 1: Selection of patients included in the analysis

Figure 2: Cause-specific survival of patients with lung metastasis of differentiated thyroid cancer

Figure 3A: ROC curve to determine cutoff values for NLR. On the basis of ROC curves, cutoff values with the best discriminatory power for NLR was 2.61

Figure 3B: Survival after the discovery of lung metastases according to the NLR

Figure 4: Survival after the discovery of lung metastases according to the risk score. Low risk, NLR <2.6 and metastatic lung tumor <10 mm in diameter; intermediate risk, NLR ≥2.6 or metastatic lung tumor ≥10 mm in diameter; high risk, NLR ≥2.6 and metastatic lung tumor ≥10 mm in diameter.
481 patients
With distant metastasis
exclusion

94 patients (19.5%)
With other than lung metastases

387 patients (80.5%)
With lung metastasis

exclusion

258 patients (66.7%)
Without RAI accumulation

129 patients (33.3%)
With RAI accumulation

exclusion

6 patients (4.7%)
Only WBS (< 100 mCi)

123 patients (95.3%)
Included patients (>100 mCi)

Figure 1: Selection of patients included in the analysis

85x73mm (600 x 600 DPI)
Figure 2: Cause-specific survival of patients with lung metastasis of differentiated thyroid cancer

85x57mm (600 x 600 DPI)
Figure 3A: ROC curve to determine cutoff values for NLR. On the basis of ROC curves, cutoff values with the best discriminatory power for NLR was 2.61.

Figure 3B: Survival after the discovery of lung metastases according to the NLR.
Figure 4: Survival after the discovery of lung metastases according to the risk score. Low risk, NLR <2.6 and metastatic lung tumor <10 mm in diameter; intermediate risk, NLR ≥2.6 or metastatic lung tumor ≥10 mm in diameter; high risk, NLR ≥2.6 and metastatic lung tumor ≥10 mm in diameter.
Table 1. Patient characteristics

| Variable                                      | n = 123        |
|-----------------------------------------------|----------------|
| Age at operation (y)                         | Median 41 (4-77) |
|                                               | <55 84 (68.3)   |
|                                               | ≥55 39 (31.7)   |
| Gender                                        | Male 33 (26.8) |
|                                               | Female 90 (73.2) |
| Pathological type                             | Papillary 83 (67.5) |
|                                               | Follicular 40 (32.5) |
| Tumor size of lung metastases (mm)            | Median 7.5 (1-40) |
|                                               | <10 70 (56.9)   |
|                                               | 10-15 30 (24.4) |
|                                               | >15 23 (18.7)   |
| Age at metastasis detection (y)               | Median 47 (6-78) |
|                                               | <55 77 (62.6)   |
|                                               | ≥55 46 (37.4)   |
| Timing of metastasis, n (%)                   | Initial 67 (54.5) |
|                                               | Developed 56 (45.5) |
| Age at the start of RAI treatment (y)          | Median 48 (7-78) |
|                                               | <55 72 (58.5)   |
|                                               | ≥55 51 (41.5)   |
| Total RAI dose (mCi)                          | 258.4 (100-831) |
| Number of RAI treatment                       | 3 (1-8)        |
| NLR                                           | 1.79 (0.74-6.5) |
| Follow-up since the diagnosis of metastasis (month) | Median 147 (14-534) |

Data are expressed as median (range) or number (percentage).

RAI, radioactive iodine; NLR, neutrophil-to-lymphocyte ratio
| Variables                              | n  | Survival, % | Univariate analysis, p-value | Multivariate analysis | p-value |
|----------------------------------------|----|-------------|------------------------------|-----------------------|---------|
|                                        |    | 5-year      | 10-year                      | 15-year               |         |
|                                        |    |             |                              |                       |         |
| Age at operation (y)                   |    |             |                              |                       |         |
| <55                                    | 84 | 100         | 100                          | 89.5                  | <0.0001 | 5.23 (0.427–164.47) | 0.214  |
| ≥55                                    | 39 | 72.2        | 67.0                         | 67.0                  |         |                     |        |
| Gender                                 |    |             |                              |                       |         |
| Male                                   | 33 | 92.8        | 86.7                         | 63.5                  | 0.3826  |                     |        |
| Female                                 | 90 | 91.2        | 91.2                         | 85.8                  |         |                     |        |
| Pathological type                      |    |             |                              |                       |         |
| Papillary                              | 83 | 95.9        | 94.1                         | 86.9                  | 0.0123  | 1.23 (0.394–4.131) | 0.7206 |
| Follicular                             | 40 | 82.8        | 82.8                         | 66.3                  |         |                     |        |
| Tumor size of lung metastases (mm)     |    |             |                              |                       |         |
| <10                                    | 70 | 96.7        | 96.7                         | 96.7                  | 0.0006  | 5.93 (1.402–44.980) | 0.0129 |
| ≥10                                    | 53 | 85.1        | 82.1                         | 60.2                  |         |                     |        |
| Age at metastasis detection (y)        |    |             |                              |                       |         |
|                | <55 | ≥55 |
|----------------|-----|-----|
| Time of lung metastasis |     |     |
| Initial         | 77  | 46  |
| Developed       | 67  | 56  |
| Age at the start of RAI treatment (y) |     |     |
| <55             | 72  | 51  |
| ≥55             | 100 | 79.2|
| NLR at first RAI |     |     |
| <2.6            | 97  | 26  |
| ≥2.6            | 95.1| 79.5|

HR, hazard ratio; 95% CI, 95% confidence interval; NLR, neutrophil-to-lymphocyte ratio; RAI, radioactive iodine
Table 3. Patient Characteristics by Risk Stratification

| Variables                      | Low n=58 | Intermediate n=51 | High n=14 | p-value |
|--------------------------------|----------|-------------------|-----------|---------|
| Age at operation (y)           | 28 (4-76) | 47 (11-77)       | 58 (6-75) | 0.0033  |
| Gender                         |          |                   |           |         |
| Male                           | 13 (22.4)| 14 (27.5)        | 6 (42.9)  | 0.3210  |
| Female                         | 45 (77.6)| 37 (72.5)        | 8 (57.1)  |         |
| Pathological type              |          |                   |           |         |
| Papillary                      | 49 (84.5)| 27 (52.9)        | 7 (50.0)  | 0.0005  |
| Follicular                     | 9 (15.5) | 24 (47.1)        | 7 (50.0)  |         |
| Age at metastasis detection (y)| 39 (9-78)| 52 (11-76)       | 60 (6-77) | 0.0089  |
| Tumor size of lung metastases (mm)| 5 (1-9)| 12 (4-31) | 15.5 (10-40) | <0.0001 |
| Timing of metastasis, n (%)    |          |                   |           |         |
| Synchronous                    | 32 (55.2)| 29 (56.9)        | 6 (42.9)  | 0.6417  |
| Metachronous                   | 26 (44.8)| 22 (43.1)        | 8 (57.1)  |         |
| Age at the start of RAI treatment (y)| 41 (9-78)| 55 (11-77) | 62 (7-78) | 0.0065  |
| Total RAI dose (mCi)           | 218.3 (100-650) | 324.7 (100-655) | 279.5 (100-831) | 0.1913 |
| NLR                            | 1.64 (0.73-2.48) | 1.97 (0.87-6.5) | 3.13 (2.62-5.64) | <0.0001 |

Data are expressed as median (range) or number (percentage).

RAI, radioactive iodine; NLR, neutrophil-to-lymphocyte ratio
| Risk Group       | n  | HR   | 95% CI          | p-value | Survival, % | 5-year | 10-year | 15-year |
|-----------------|----|------|-----------------|---------|-------------|---------|---------|---------|
| Low risk        | 58 | ref  |                 |         | 97.9        | 97.9    | 97.9    |
| Intermediate risk| 51 | 6.99 | (1.19–132.00)   | 0.0292  | 91.1        | 91.1    | 79.7    |
| High risk       | 14 | 41.72| (7.34–782.83)   | <0.0001 | 69.6        | 59.7    | 19.9    |

HR, hazard ratio; 95% CI, 95% confidence interval; ref, reference