Original Article

Predictive value of the monocyte-to-high-density lipoprotein ratio in the prognosis of non-small cell lung cancer patients after surgery

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Background: Due to the poor prognosis of non-small cell lung cancer (NSCLC) patients, precise and reliable biomarkers are urgently needed to predict the prognosis in NSCLC patients after radical lung surgery. Hence, this study sought to investigate the correlation between the monocyte-to-high-density lipoprotein ratio (MHR) and overall survival (OS) in NSCLC patients after surgery.

Methods: This retrospective study analyzed clinical data, including MHR, from NSCLC patients undergoing radical surgery. OS was calculated to evaluate the prognosis of the NSCLC patients. The association between the MHR and OS was analyzed. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate the 3- and 5-year predictive value of the MHR for prognosis after surgery.

Results: In total, 256 patients were enrolled in this study. All patients had a follow-up for more than 5 years. The prognosis of the patients with a higher MHR (>0.3) was worse than that of the patients with a lower MHR (≤0.3) (P<0.001). The univariate Cox survival analysis showed that the MHR, surgery time, tumor (pT) stage, lymph node (pN) stage, and sex were all significantly associated with the risk of death in patients with NSCLC. The multivariate Cox survival analysis showed that the MHR [hazard ratio (HR) =24.837, 95% confidence interval (CI): 7.265–84.911], T stage, N stage, and surgery time were prognostic factors for NSCLC patients after surgery. The stratified analysis, which excluded patients with tumors *in situ*, showed that the MHR (HR =27.097, 95% CI: 8.081–90.877), surgery time, and pN stage significantly increased the risk of death in NSCLC patients. The area under the ROC curve (AUCROC) values of the MHR in predicting the 3- and 5-year survival of the NSCLC patients after surgery were 0.758 and 0.760, respectively.

Conclusions: The MHR was found to be an independent predictor of OS in NSCLC patients after radical surgery. Early monitoring and reducing the MHR may be of great significance in preventing disease recurrence and improving patient prognosis.

Keywords: Non-small cell lung cancer (NSCLC); monocyte-to-high-density lipoprotein ratio (MHR); prognosis; overall survival (OS); radical surgery

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Introduction

Non-small cell lung cancer (NSCLC) is the most aggressive malignant tumor worldwide, and accounts for more than 85% of all lung cancer cases (1-3). The annual incidence and mortality rates of NSCLC are similar, and its 5-year overall survival (OS) rate is less than 15% (1,3). At present, surgical resection plays a pivotal role in the treatment of early-stage NSCLC, and adjuvant treatment is not recommended for stage I–IIA NSCLC patients after radical resection (4). However, a substantial number of early-stage NSCLC patients who undergo surgical resection experience early recurrence after radical surgical treatment and have low OS (5,6). Patients predicted to have poor OS could derive significant benefits from early intervention. Therefore, precise and reliable biomarkers are urgently needed to be identified to predict the risk of death in patients with NSCLC after radical surgery.

Inflammation plays a critical role in tumor occurrence, and metastasis, and strong systemic inflammation indicates faster tumor progression and a shorter survival time (7). The level of peripheral blood monocytes (MONs), which differentiate into tumor-associated macrophages (TAMs) with pro-tumorigenic functions, and promote tumor growth and metastasis, can reflect the severity of inflammation in both systemic and tumor microenvironments (8,9). High-density lipoprotein (HDL) is considered a protective factor against NSCLC, as it enhances anti-tumor immune responses, inhibits tumor progression and angiogenesis, and regulates signal transduction (10-12).

The monocyte-to-high-density lipoprotein ratio (MHR), which has been identified as a novel inflammatory marker, plays an important role in many tumors, including thyroid (13), breast (14), gastric (15), and colorectal cancers (16). However, it is not yet known whether MHR correlates with prognosis of NSCLC patients after radical surgery. Hence, this study aims to investigate the relationship between the MHR and the prognosis of NSCLC patients after radical surgery, and to determine the best index for predicting the prognosis of these patients. We present this article in accordance with the TRIPOD reporting checklist (17) (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-171/rc).

Highlight box

Key findings

- The monocyte-to-high-density lipoprotein ratio (MHR) can be used to predict the survival of non-small cell lung cancer (NSCLC) patients after surgery.

What is known, and what is new?

- MHR can be used to predict the survival of patients with many types of cancers.
- In this study, we confirmed that MHR can be used to predict the survival of NSCLC patients after surgery.

What is the implication, and what should change now?

- MHR can be used to identify high-risk NSCLC patients after surgery, and to inform decisions about treatment regimens. We may use MHR to identify the high-risk NSCLC patients after surgery.

Methods

Patient enrollment

NSCLC patients were enrolled in this single-center (Beijing Chaoyang Hospital) retrospective study from August 2016 to December 2017. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have a pathologically confirmed diagnosis of NSCLC; and (II) have undergone surgical R0 resection for NSCLC. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had preoperative complications of acute inflammation or anti-inflammatory treatment within 1 month before surgery; (II) had received lipid-lowering treatment within 6 months before surgery; (III) other types of malignant tumors, or had neo-adjuvant treatment; (IV) had a combination of severe hepatic and renal dysfunction; and/or (V) had missed an MHR value during NSCLC surgery, or had missing clinical or follow-up data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Beijing Chaoyang Hospital (No. 2024-ke-28) and the written consent for this retrospective analysis was waived.

Data collection

Clinical data of the patients, including sex, age, body mass index (BMI, kg/m^2), albumin (ALB, g/L), blood cholesterol (mmol/L), HDL (mmol/L), low-density lipoprotein (LDL, mmol/L), blood triglyceride (TG, mmol/L), MONs (10^9/L), MHR, tumor location, tumor (pT) stage, lymph node (pN) stage, metastasis (pM) stage, pathological type, tumor-lymph node-metastasis (pTNM) stage (TNM staging was performed using the American Joint Committee on Cancer TNM staging system, 9th edition), surgical

approach, operation time, and perioperative bleeding, were retrospectively collected from the electronic medical records system, all the blood cell mentioned were expressed as absolute counts. If patients had synchronous multiple primary lung cancers and underwent multiple resections during surgery, the surgical approach and pT stage were classified based on the primary lung cancer with the highest pT stage.

The fasting blood of the patients was collected within 7 days before surgery for testing. Postoperative pathological specimens were examined by the pathology Department.

OS assessment

OS was defined as the time from the date of surgery until death from any cause or the last follow-up date. Lung cancer specific survival was not used since some patients' death reason was unknown. Follow-up was performed every 6 months after surgery using a combination of outpatient and telephone visits.

Statistical analysis

The statistical analyses were conducted using R Studio (version 1.3.959; R Project for Statistical Computing, Vienna, Austria; https://www.r-project.org). A P value <0.05 was considered statistically significant. The patients were divided into the following two groups based on the median MHR: the low-MHR group, and the high MHR group. Kaplan-Meier curves were used to analyze the effect of the MHR on OS. Univariate and multivariate Cox survival analyses were used to identify the prognostic predictors for NSCLC patients after surgery. We also excluded the patients diagnosed with carcinoma in situ and performed the analysis on the rest of the patients, as such patients had an indisputably good prognosis, and univariate and multivariate Cox survival analyses were conducted to identify the prognostic factors. All the results are expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). The value of the MHR in predicting the prognosis of NSCLC patients at both 3 and 5 years was evaluated using receiver operating characteristic (ROC) curves. The area under the ROC curve (AUROC) was used to assess the accuracy of the cut-off value. Data are expressed as the mean ± standard deviation for the continuous variables if normally distributed, and as percentage for the categorical variables. Clinical data were analyzed using the Pearson χ^2 test for the categorical data, and the Wilcoxon rank-sum test for the continuous data if non-normally distributed. A kappa consistency analysis was used for the intra- and inter-cohort consistency analysis.

Results

Demographic and clinical characteristics of patients

A total of 265 NSCLC patients who had underwent surgery were enrolled in this retrospective cohort study. An enrollment flow chart for the study is provided in *Figure 1*. The characteristics of the study cohort are set out in *Table 1*. The median follow-up time was 80.5 months, and 58 (21.9%) patients died during the follow-up period. Among all the patients, 26 (9.8%) had ipsilateral primary lung tumors located in different lobes on the same side, which were all resected simultaneously. To reduce bias in the multivariable prognosis analysis, the variable level was shrunk by classifying multiple primary lung cancers as the lung cancer with the highest T stage.

Correlations between the MHR and OS in NSCLC patients

To investigate the relationship between MHR and prognosis, the patients were categorized into two groups according to the median MHR (≤0.3 and >0.3). The Kaplan-Meier curve analysis showed that MHR was a significant predictor of the risk of death (log rank P<0.001), and the 5-year survival rates were 92.73% for patients with an MHR ≤0.3 and 68% for patients with an MHR >0.3 (*Figure 2*).

Correlations between the MHR and the NSCLC patient's prognosis of clinical parameters

In the univariate cox analysis, MHR (HR =52.22, 95% CI: 20.19–135.10, P<0.001) was associated with a significant increase death risk for NSCLC patients. Further, surgery time, pT stage, pN stage, pTNM stage, and sex were also significantly associated with the prognosis of NSCLC patients. However, no correlation between the remaining variables and the risk of death was found (P>0.05) (*Table 2*).

Factors with a P value <0.05 were included in the multivariate Cox survival analysis. To avoid the multicollinearity and due to the small size of this study, pT stage and pN stage (rather than pTNM stage) were included in the cox multivariate analysis. The results showed that MHR (HR =24.837, 95% CI: 7.265–84.911),

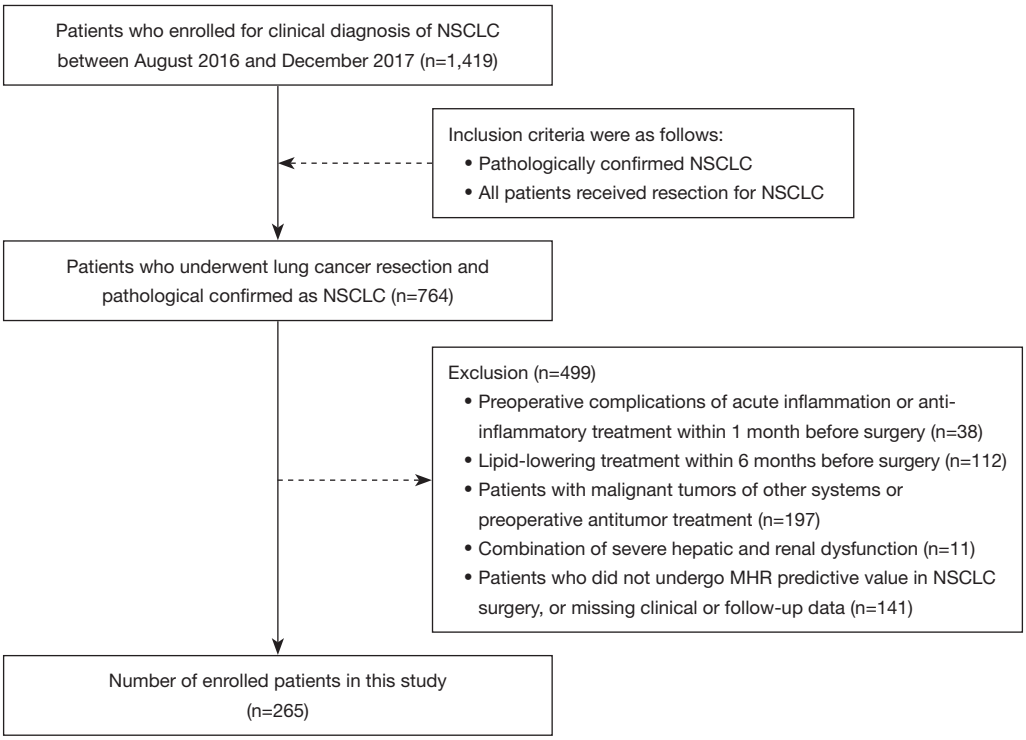

Figure 1 Flow chart of patient selection. MHR, monocyte-to-high-density lipoprotein ratio; NSCLC, non-small cell lung cancer.

pT stage, pN stage, and surgery time remained independent predictors of prognosis (*Table 3*). Further, after excluding patients with tumors *in situ*, MHR (HR =27.097, 95% CI: 8.081–90.867), surgery time, and pN stage were also found to be prognostic factors for NSCLC patients (*Table 3*).

Analysis of the 3- and 5-year predictive value of the MHR in NSCLC patients

The value of MHR in predicting the survival of NSCLC patients at 3 and 5 years was analyzed using ROC curves. For 3-year OS, the AUROC was 0.758 (95% CI: 0.679–0.890, P<0.001), and the optimal cut-off value of the MHR was 0.562 (*Figure 3A*). For 5-year OS, the AUROC was 0.760 (95% CI: 0.682–0.851, P<0.001), and the optimal cut-off value of the MHR was 0.480 (*Figure 3B*). The optimal cut-off value of both 3- and 5-year OS were different from the median MHR value 0.3, which we used as the cutoff value to divide the all MHR into high and low group.

Discussion

In this single-center retrospective cohort study, we sought to investigate the relationship between MHR and prognosis of NSCLC patients. We found that MHR was a prognostic predictor for NSCLC patients, the higher MHR, the poorer the patient prognosis. Further, we also found that operation time and gender were correlated with prognosis.

In previous studies, peripheral MONs was shown to reflect the severity of inflammation in both systemic and tumor microenvironments (18,19). Furthermore, peripheral MONs was also shown to decrease the survival of patients with various cancers, including hepatocellular carcinoma, pancreatic cancer, and colorectal cancer (13,19-26). Research has shown that MON counts are significantly increased in NSCLC patients, and are negatively correlated with survival (27-30). In previous studies, MONs has been reported to play a complex role in tumor microenvironment and affect the prognosis of lung cancer patients (31-34). However, in this study, the univariate analysis showed that MONs was not a risk factor for OS in NSCLC patients (P=0.51).

HDL plays an important role in cholesterol clearance and thromboembolism (35-37), and has been shown to be correlated with the risk of developing various carcinomas (35,38-42). HDL is considered a protective factor against

Table 1 Clinical and pathological characteristics of non-small cell lung cancer study patients

Clinical characteristics	Total (N=265)
Gender	
Male	127 (47.9)
Female	138 (52.1)
Age (years)	60.1±9.3 (31–85)
Operation time (minutes)	174.7±50.1 (60–330)
Preoperative bleeding (mL)	190.3±250.4 (5–2,600)
BMI (kg/m^2)	23.9±3.3 (12.4–36.4)
ALB (g/L)	41.6±4.2 (27.6–50.4)
CHOL (mmol/L)	4.7±1.0 (2.25–8.53)
HDL (mmol/L)	1.3±0.3 (0.7–2.4)
LDL (mmol/L)	2.9±0.8 (1.2–6.3)
TG (mmol/L)	1.4±0.8 (0.35–6.05)
MONs (10^9/L)	0.4±0.2 (0.12–1.26)
MHR	0.4±0.2 (0.04–1.24)
Survival status (till the last follow-up)	
Alive	207 (78.1)
Dead	58 (21.9)
3rd-year survival status	
Alive	237 (89.4)
Dead	28 (10.6)
5th-year survival status	
Alive	221 (83.4)
Dead	44 (16.6)
Overall survival (till the last follow-up, patients still alive) (months)	72.8±21.5 (64–94)
Surgical approach	
Lobectomy	216 (81.5)
Wedge resection	19 (7.2)
Segmentectomy	4 (1.5)
Pneumonectomy	5 (1.9)
Bi-lobectomy	1 (0.4)
Lobectomy & wedge resection	10 (3.8)
Multiple wedge resection	10 (3.8)
Tumor location	
Left upper lobe	68 (25.7)
Left lower lobe	37 (14.0)
Right upper lobe	80 (30.2)
Right middle lobe	10 (3.8)
Right lower lobe	44 (16.6)
Left upper/lower lobe	7 (2.6)
Right upper/middle lobe	3 (1.1)
Right upper/lower lobe	7 (2.6)
Right middle/lower lobe	7 (2.6)
Right upper/middle/lower lobe	2 (0.8)
Tumor cell type	
Adenocarcinoma	212 (80.0)
Squamous cell carcinoma	52 (19.6)
Adeno-squamous carcinoma	1 (0.4)
T stage	
Tis	51 (19.2)
T1	161 (60.8)
T2	41 (15.5)
T3	9 (3.4)
T4	3 (1.1)
N stage	
N0	203 (76.6)
N1	23 (8.7)
N2	39 (14.7)
TNM	
TisN0M0	51 (19.2)
Stage I	128 (48.3)
Stage II	43 (16.2)
Stage III	43 (16.2)

Continuous variables are presented as mean ± standard deviation (range), and categorical variables are described as number (%). TNM staging was performed using the American Joint Committee on Cancer TNM staging system, 9th edition. ALB, albumin; BMI, body mass index; CHOL, blood cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio; MONs, monocytes; N, lymph node; TG, blood triglyceride; T, tumor; Tis, tumor in situ; TNM, tumor-lymph node-metastasis.

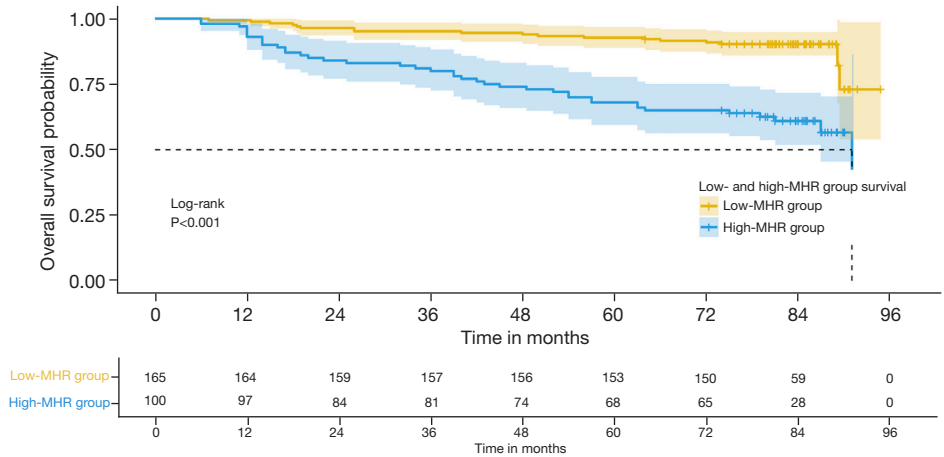

Figure 2 Kaplan-Meier survival analysis stratified by MHR. Patients in the low-MHR group demonstrated significantly improved survival compared to the high-MHR group (P<0.001). MHR, monocyte-to-high-density lipoprotein ratio.

Table 2 Univariate survival analysis of overall survival

Clinical factors	P value	Univariate analysis		
		HR	95% CI	
			Lower limit	Upper limit
Gender	0.02*	0.538	0.316	0.9158
Age	0.27	1.016	0.988	1.045
Operation time	0.003*	1.007	1.002	1.012
Perioperative bleeding	0.15	1.001	1.000	1.001
BMI	0.37	1.035	0.960	1.115
Surgical approach	0.42	1.196	0.773	1.851
ALB	0.37	0.972	0.914	1.034
CHOL	0.34	0.882	0.681	1.142
HDL	0.91	0.957	0.449	2.039
LDL	0.72	0.943	0.685	1.298
TG	0.39	0.862	0.615	1.208
MONs	0.51	1.69	0.357	8.018
MHR	<0.001*	52.22	20.19	135.10
Tumor cell type	0.14	1.528	0.875	2.667
T stage	<0.001*	1.966	1.479	2.613
N stage	<0.001*	2.272	1.716	3.008
TNM stage	<0.001*	2.700	2.048	3.560

TNM staging was performed using the American Joint Committee on Cancer TNM staging system, 9th edition. *, P<0.05. ALB, albumin; BMI, body mass index; CHOL, blood cholesterol; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein; MHR, monocyte-to-high-density lipoprotein ratio; MONs, monocytes; N, lymph node; TG, blood triglyceride; T, tumor; TNM, tumor-lymph node-metastasis.

Table 3 Multivariate survival analysis of overall survival of all patients, and patients without TisN0M0

Clinical factors	Multivariate analysis of all patients (n=265)				Multivariate analysis, excluding TisN0M0 patients (n=214)			
	HR	95% CI		P value	HR	95% CI		P value
		Lower limit	Upper limit			Lower limit	Upper limit	
Gender	1.097	0.624	1.927	0.75	1.213	0.690	2.130	0.50
Operation time	1.007	1.002	1.012	0.005*	1.007	1.002	1.012	0.01*
MHR	24.837	7.265	84.911	<0.001*	27.097	8.081	90.867	<0.001*
T stage	1.471	1.048	2.065	0.03*	1.161	0.772	1.744	0.47
N stage	1.412	1.020	1.956	0.04*	1.429	1.009	1.837	0.045*

T stage and N stage were performed using the American Joint Committee on Cancer TNM staging system, 9th edition. *, P<0.05. CI, confidence interval; HR, hazard ratio; MHR, monocyte-to-high-density lipoprotein ratio; N, lymph node; T, tumor; TNM, tumor-lymph node-metastasis.

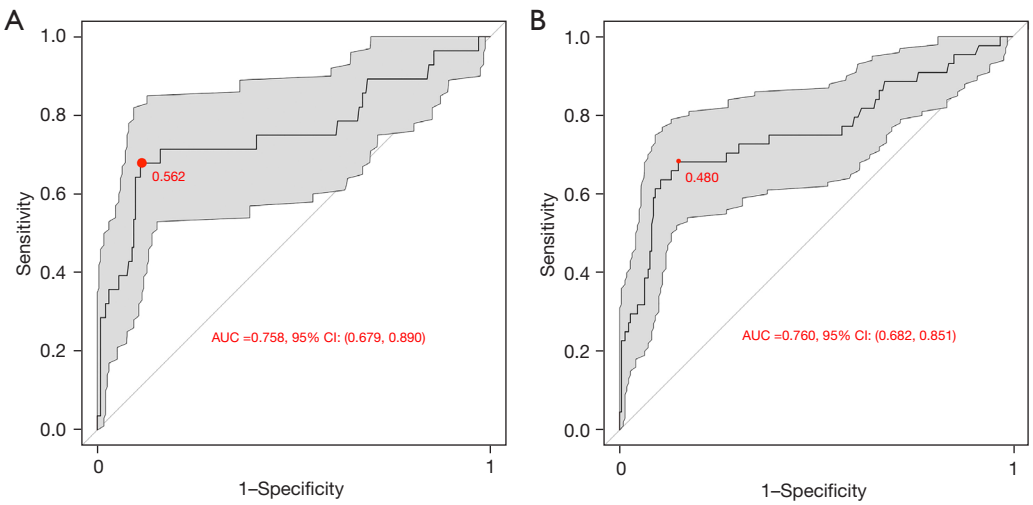

Figure 3 ROC curve analysis of the prediction of death based on the MHR. (A) ROC curve analysis of the prediction of death at 3 years based on the MHR. (B) ROC curve analysis of the prediction of death at 5 years based on the MHR. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; MHR, monocyte-to-high-density lipoprotein ratio.

tumors, and research has shown that lower HDL levels are associated with higher TNM stages and a higher likelihood of metastasis (42). Further, HDL plays an important role in the immune regulation of tumors (43) by inducing cholesterol depletion in TAMs to weaken pro-tumorigenic effects (44). Moreover, HDL also enhances the anti-inflammatory effects of neutrophils by promoting the activation of cluster of differentiation (CD)8$^+$ and CD4$^+$ T cells, and modulating the functions of antigen-presenting cells and their complements (45,46). However, in our study, the univariate analysis showed that preoperative HDL levels were not correlated with the OS of NSCLC patients, which is inconsistent with the findings of previous studies (47,48). However, this inconsistency may be due to the small sample size of the present study.

In this study, we used MHR (rather than the MONs or HDL alone) to predict patient prognosis for a number of reasons. Notably, while single indexes, like MONs or HDL, have been reported to be predictors of prognosis, these predictors have not been shown to perform well. Conversely, we hypothesized as a predictor of NSCLC prognosis, the MHR would perform well. Indeed, the MHR was shown to be an independent predictor of NSCLC in both the univariable and multivariable analyses.

To reduce the confounding factors in the survival analysis, we excluded patients with stage pTisN0M0, as their concomitant outstanding survival might have affected the univariable and multivariable analyses. In the stratification analysis, MHR was also found to be a prognostic predictor for NSCLC patients, such that the higher the MHR, the worse the OS of the patients. The HR of the MHR in the multivariable analysis of the whole patient cohort was lower than that of the cohort that excluded the TisN0M0, which indicates that the MHR was more effective at predicting the prognosis of advanced NSCLC patients.

Previous studies have reported that an advanced stage, incomplete resection, and a positive resection margin are poor prognostic factors (5,49). Notably, we found that surgery time was an independent predictor of OS. Specifically, we found that the longer the surgery time, the poorer the prognosis of the patients, which has not been previously report. We try to figure out why surgery time is an independent prognosis factor and divided all patients into two cohort (short surgery time *vs.* long surgery time) by median surgery time (175 minutes) to compare the tumor/surgery related clinic data difference. In short surgery time cohort, the intraoperative bleeding is less than long surgery time cohort (116.9 *vs.* 263.1 mL, P<0.01). What's more, patients in the long surgery time cohort exhibited more advanced stage than those in the short surgery time cohort. The proportions of pStage III, pStage II, pStage I and pTisN0M0 was 11.4%, 15.9%, 49.2% and 23.5%, respectively in the short surgery time cohort, and 21.1%, 16.7%, 48.1%, 14.3% in the long surgery time cohort, respectively. As for surgery approach, there is no difference between the short and long surgery time cohort because most patients underwent lobectomy (80.3% *vs.* 82.7%). As surgery time may exhibit multicollinearity with pTNM stage and intraoperative bleeding, we consider that future studies with larger cohorts are needed to confirm whether surgery time is an independent prognostic factor for patients undergoing lung cancer surgery.

To avoid multicollinearity, MONs or HDL were not included as variables in the Cox multivariable analysis, as doing so could have affected the analysis of the MHR. Further, due to the small size of this study, we included T stage and N stage (rather than TNM stage) in the prognostic analysis.

This study has a number of limitations. First, this was a single-center retrospective cohort study with a small sample size; thus, selection bias was inevitable, and larger size, multi-center studies need to be conducted to confirm the results. Second, postoperative adjuvant therapy information was not included in this study, which affected the prognosis results. Third, some confounders, such as smoking status, comorbidity, and postoperative complications, are difficult to control, which might have affected the study.

Conclusions

Our study found that MHR was an independent predictor of OS in surgically treated NSCLC patients. Due to its convenience and effectiveness of this biomarker, it can help identify high-risk patients, predict prognosis and support treatment decisions.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-171/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-171/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-171/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Beijing Chaoyang

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