Prognostic significance of advanced lung cancer inflammation index (ALI) in multiple myeloma patients – a retrospective study

Junxia Huang
Department of Hematology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University

Juanjuan Hu
Department of Hematology, Affiliated Hospital of Qingdao University

Yan Gao
Department of Hematology, Affiliated Hospital of Qingdao University

Fanjun Meng
Department of Hematology, Affiliated Hospital of Qingdao University

Tianlan Li
Department of Hematology, Affiliated Hospital of Qingdao University

Chunxia Mao
Department of Hematology, Affiliated Hospital of Qingdao University

Shanshan Liu
Department of Hematology, Affiliated Hospital of Qingdao University

Xue Shi
Department of Hematology, Affiliated Hospital of Qingdao University

Wei Wang
Department of Hematology, Affiliated Hospital of Qingdao University

Xianqi Feng (qdfxq2005@163.com)
Department of Hematology, Affiliated Hospital of Qingdao University

Research Article

Keywords: multiple myeloma, prognosis, advanced lung cancer inflammation index, neutrophil-to-lymphocyte ratio, body mass index

DOI: https://doi.org/10.21203/rs.3.rs-288915/v1

Abstract

Background: Advanced lung cancer inflammation index (ALI) is known to predict the overall survival of patients having some solid tumors or B-cell lymphoma. The study investigates the predictive value of ALI in multiple myeloma (MM) patients and the correlation between ALI and prognosis.

Methods: A database of 269 MM consecutive patients who underwent chemotherapy between December 2011 and June 2019 in the Affiliated Hospital of Qingdao University was reviewed. ALI cut-off value calculated before the initial chemotherapy and post 4 courses treatment were identified according to the receiver operating characteristic (ROC) curve, and its association with clinical characteristics, treatment response, overall survival (OS), and progression-free survival (PFS) were assessed.

Results: Patients in the low ALI group (n=147) had higher risk of β2 microglobulin elevation, more advanced ISS (International Classification System stage), and TP53 gene mutation, with significantly lower median overall survival (OS; 36.29 vs. 57.92 months, P = 0.010) and progression-free survival (PFS; 30.94 vs. 35.67 months, P = 0.013). Independent risk factors influencing the OS of MM patients were ALI (P = 0.007), extramedullary infiltration (P = 0.001), TP53 (P = 0.020), Plt (P = 0.005), and bone destruction (P = 0.024). ALI (P = 0.005), extramedullary infiltration (P = 0.004), TP53 (P = <0.001), Plt (P = 0.017), and complex chromosome karyotype (P = 0.010) were independent risk factors influencing the PFS of MM patients.

Conclusions: ALI is a potential independent risk factor predicting the prognosis of newly diagnosed MM patients.

Background

Multiple myeloma (MM) is a malignant hematological tumor, exhibiting the plasma cells proliferation due to different genetic mutations leading to aggressive tumor growth, with the prognosis of the disease (1). Correct and prompt staging of the disease in MM patients is essential for proper treatment and evaluation of the prognostic factors (2). GLOBOCAN 2018 statistics reported that there were 159,985 new MM cases with 106,105 cancer deaths globally in 2018 (3). In China, 16,500 new cases and 10,300 deaths of multiple myeloma were reported in 2016, and the age-standardized incidence rates and mortality rates per 100,000 population were 1.03 (95% UI, 0.88–1.17) and 0.67 (95% UI, 0.59–0.77), respectively (4). Though advanced therapeutic strategies like use of proteasome inhibitors, immunomodulator drug-based chemotherapy, combined with autologous stem cell transplantation (ASCT), increased the survival of MM patients, yet it remains incurable at large (5).

Disease prognosis in MM patients do vary significantly. Currently, the most common staging systems of MM were Durie-Salmon staging system (D-S), the International Staging System (ISS), and the Revised-International Staging System (R-ISS) (6–8). D-S staging system addresses mainly on the variables correlate with myeloma mass, but the biologic variability of the disease is not considered (1). Though R-ISS is powerful prognostic staging system, yet its application is primarily for risk stratification of patients

in clinical trials (1). A study has reported that ISS and D-S staging system is better for characterizing and stratifying MM patients, and the focal pattern on MRI associates with poorer survival (9). Also, International Myeloma Working Group (IMWG) risk stratification, and the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) have been widely used (10, 11). The mSMART system proposed by the Mayo clinic uses cytogenetic analysis as the foundation for assessment (11). Though the staging systems were updated, yet they are not applicable for every single patient with different prognostic factors. So, it is essential to identify new predictors of prognosis, as well as to develop more appropriate staging criteria and individualized treatment strategies. Recently, based on the nomogram assessment, age at diagnosis, clonal bone marrow plasma cells, serum lactate dehydrogenase, serum β2-microglobulin, and del (17p) were identified as independent risk factors for overall survival (OS) (5). Generally, prognosis of MM patients were assessed based on clinical features, morphology, molecular biology, and cytogenetics, which is quite time consuming and expensive. So, simple, and reliable prognostic indicators for newly diagnosed MM patients is highly essential.

Advanced lung cancer inflammation index (ALI) proves to be a prognostic index for non-small-cell lung cancer (NSCLC) and calculated as body mass index (BMI) x serum albumin (ALB) / neutrophil to lymphocyte ratio (NLR) (12). In meta-analysis study on lung cancer patients, low ALI before treatments is known to be an indicator for poor prognosis (13). Similarly, low ALI index showed a poor prognosis for advanced intrahepatic cholangiocarcinoma (14). Pretreatment ALI acts as a significant independent predictor of early progression in advanced NSCLC patients treated with nivolumab (15). In small-cell lung cancer, there was no additional prognostic value of modified ALI (mALI) using CT-determined L3 muscle index beyond original ALI (16). So, ALI act as a promising biomarker for different cancer prognosis in recent years.

Earlier studies have shown that medullar immunological microenvironment of MM act as an important influencing factor inducing the drug resistance, recurrence, and refractoriness in MM (17). But the clinical indicator that could well reflect the medullar immunological microenvironment is yet to be identified. The neutrophil/lymphocyte ratio (NLR) is said to be a predictor of PFS and OS in MM patients when treated upfront with novel agents. The study had shown that 5-year PFS and OS were 18.2 and 36.4 % for patients with NLR $\geq$ 2 versus 25.5 and 66.6 % in patients with NLR < 2, respectively (18). Another study also indicated that at diagnosis, patients with NLR < 2 experienced higher OS than patients with a NLR $\geq$ 2 (19). The method of calculating ALI shows that ALI is positively associated albumin level and BMI, but negatively associated with NLR, while albumin and NLR are strongly associated with the prognosis of MM patients (18, 19). Therefore, ALI may be associated with the prognosis of MM patients. Till date, no studies have demonstrated the predictive and assessment value of ALI in diagnosing and predicting prognosis of MM patients. The present study retrospectively analyzed the clinical data of 269 newly diagnosed MM patients from a single hospital to understand the association of ALI with clinical characteristics, treatment response, and prognosis of MM patients. The findings from this study emerged to develop a more precise subgrouping model involving clinical characteristics, biochemical indicators, and genetics, which in-turn helps in individualized treatment.

Methods

Patients

We retrospectively identified diagnosed consecutive MM patients treated in the Affiliated Hospital of Qingdao University between December 2011 and June 2019. The inclusion criteria were as follows: 1) age > 18 years old; 2) confirmed with MM (20); and 3) newly diagnosed, treatment-naive MM patients. The exclusion criteria were as follows: 1) with evidence of active infection at the initial diagnosis; 2) accompanied with chronic inflammatory diseases, such as rheumatoid arthritis, chronic inflammatory bowel diseases, and vasculitis; 3) accompanied with chronic renal or liver diseases; and 4) accompanied with other solid tumors or lymphoma. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL28913) and informed consents were waived due to the inherent obstacle of retrospective analysis.

Data collection

The following clinical data were collected from the newly diagnosed MM patients before the first chemotherapy: sex, age, hemoglobin (Hb), platelet count (PLt), β2 microglobulin (β2MG), creatinine (Cr), lactic dehydrogenase (LDH), percentage of plasma cells in bone marrow, bone destruction, extramedullary infiltration (EMD), calcium (Ca), stages, types, fluorescence *in situ* hybridization (FISH) results, and treatment efficacies.

Treatment regimens

Different chemotherapy regimens were selected based on the diagnostic results. The chemotherapy regimens included the following: VD (bortezomib + dexamethasone), VAD (bortezomib + doxorubicin + dexamethasone), VDT (bortezomib + dexamethasone + thalidomide), VCD (bortezomib + cyclophosphamide + dexamethasone), PAD (bortezomib + liposomal doxorubicin + dexamethasone), RD (lenalidomide + dexamethasone), VRD (bortezomib + lenalidomide + dexamethasone), and VAD (vindesine + adriamycin + dexamethasone).

Calculation of ALI

ALI was calculated according to the following equation: ALI = body mass index (BMI) × albumin (g/dL) / NLR (21). The ALI value was calculated before the initial chemotherapy and after 4 courses treatment. They were grouped as follows: subgroup 1: low pre- and post- treatment ALI; subgroup 2: low pre-treatment but high post-treatment ALI; subgroup 3: high pre-treatment but low post-treatment ALI; and subgroup 4: high pre- and post- treatment ALI.

Follow up

The patients were followed up once a month until October 30, 2019, by telephone, or clinic visits with a minimum period of 4-months. The treatment efficacies were assessed after 4 courses treatments,

according to the International Myeloma Working Group consensus criteria (22). Overall survival (OS) was defined as the time from disease diagnosis to the end of follow up or death. Progression-free survival (PFS) was defined as the time from disease diagnosis to disease progression, recurrence after CR, and end of follow up, or death.

Statistical analysis

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for the statistical analysis. Using descriptive statistics, the patients' details were summarized, such as mean, median and range for quantitative variables and frequencies for qualitative variables. Data were expressed as means ± standard deviations or median (range). Receiver operating characteristic (ROC) curve was used to identify the cut-off value of ALI. The rates were compared between the two groups by Chi-square test or Fisher exact test. Quantitative data were compared by independent t-test or non-parametric Mann-Whitney U test. The survival curves were plotted by Kaplan-Meier method, and the survival analysis was assessed by Log-rank test. For multivariate regression analysis, the variables with statistical significances in univariate analysis were included in the Cox proportional hazard model by forward selection. $P < 0.05$ was considered statistically significant for all the analyses.

Results

Comparison of ALI group among MM patients

Among the 269 MM patients included in this study, there were 166 males (61.7%) and 103 females (38.3%), and the median age of them was 64 (30 - 88) years. The median ALI of the 269 patients was 43.596 (2.7 - 324.6). We treated ALI as independent variable. According to the sensitivity and specificity in the ROC curve, Youden index was calculated. and the cut-off value for ALI was defined as the one with corresponding largest Youden index. The ALI, which is a continuous variable, was used as the test variable, and diagnosed with MM was used as the state variable. The cut-off value of ALI was 45.8 (95% CI 0.63 - 0.74), for which the area under the ROC curve was 0.685, and the sensitivity and specificity was 82.3% and 53.8%, respectively (Figure 1). The patients were further divided into the low ALI group (ALI ≤ 45.8, n =147) and high ALI group (ALI > 45.8, n=122). On comparing with the high ALI group, more patients in the low ALI group were with higher β2 microglobulin levels (P=0.038) and later ISS stages (P=0.039). The other clinical characteristics of the patients were not significantly different between the two groups (P > 0.05) (Supplementary Table 1).

Chemotherapy responses in the high and low ALI groups

Among the 269 MM patients, 231 (85.87%) received bortezomib-based chemotherapy, and 38 (14.13%) received conventional chemotherapy. The treatment regime did not show any significant different between the high and low ALI groups. The rate of ≥ VGPR and ≥ PR were 53.3% and 71.8% in the 269 patients after 4 courses treatments. In detail, the rate of ≥ VGPR and ≥ PR were 56% and 68.5% in the

low ALI group, and 50.4% and 75.4% in the high ALI group, respectively, but it does not show statistically difference between the two groups (Supplementary Table 1).

Association between ALI and cytogenetics of MM patients

Among the 269 patients, 144 received FISH examination. The results of the FISH examination showed that patients with low ALI at admission were with higher risk of carrying positive TP53 mutation, compared to the ones with high ALI (P = 0.032). However, IgH, RB-1, and 1q were not significantly different between the two groups (Table 1).

Survival analysis

During the follow up, 198 of the 269 MM patients survived, while the other 71 died. The median survival time of the MM patients was 18.3 months. In detail, 98 and 24 patients in the high ALI group survived and died, respectively, and the median survival time was 19.8 months; while 100 and 47 patients in the low ALI group survived and died, respectively, and the median survival time was 13 months. Survival analysis showed that the OS (log-rank test, P = 0.011) and PFS (log-rank test; P = 0.015) in the low ALI group were significantly lower than in the high ALI group (Figure 2). Univariate COX regression analysis showed that ALI (P = 0.011), extramedullary infiltration (P <0.001), age (P = 0.047), PLT (P = 0.002), LDH (P = 0.002), TP53 (P = 0.003), complex chromosome karyotype (P = 0.001), and bone destruction (P = 0.026) were risk factors influencing the OS of MM patients. Multivariate Cox regression analysis showed that ALI (P = 0.007), extramedullary infiltration (P = 0.001), TP53 (P = 0.020), PLT (P = 0.005), and bone destruction (P = 0.024) were independent risk factors influencing the OS of MM patients (Table 2). In addition, univariate COX regression analysis showed that ALI (P = 0.005), extramedullary infiltration (P = 0.004), age (P = 0.040), Hb (P = 0.024), PLT (P = 0.001), LDH (P = 0.024), TP53 (P < 0.001), and complex chromosome karyotype (P = 0.026) were the risk factors influencing the PFS of MM patients. Multivariate Cox analysis showed that ALI (P = 0.005), extramedullary infiltration (P = 0.004), TP53 (P < 0.001), PLT (P = 0.017), and complex chromosome karyotype (P = 0.010) were the independent risk factors influencing the PFS of MM patients (Table 3).

Association of ALI change with OS and PFS

The patients were divided into 4 subgroups as follows according to the ALI changes after 4 courses treatments, comparing with the pre-treatment ALI: 1) subgroup 1: low pre- and post- treatment ALI (n = 111, 42.7%); 2) subgroup 2: low pre-treatment but high post-treatment ALI (n = 28, 10.8%); 3) subgroup 3: high pre-treatment but low post-treatment ALI (n = 67, 25.8%); and 4) subgroup 4□high pre- and post-treatment ALI (n = 54, 20.8%). The treatment responses in different subgroups were assessed, and the results showed that the overall response rate (ORR) was significantly higher in the subgroup 2 than subgroups 1 and 3 (subgroup 1 vs. subgroup 2 vs. subgroup 3: 68.5% vs. 96.4% vs. 71.6%, P = 0.016), but was not significantly different between other subgroups. The very good partial response rate (VGPR) was significantly higher in the subgroup 2 than subgroups 1, 3, and 4 (subgroup 1 vs. subgroup 2 vs. subgroup 3 vs. subgroup 4: 51.4% vs. 78.6% vs. 46.3% vs. 53.7%, P < 0.001), but was not significantly

different between other subgroups (Table 4). Based on the Chi square data, a significant connectivity between subgroups 1 and 2 (P = 0.002), subgroups 1 and 4 (P = 0.001), and subgroups 2 and 3 (P = 0.017) with respect to overall survival was observed (Table 5). With respect to PFS, a significant connectivity between subgroups 1 and 2 (P = 0.002), subgroups 1 and 4 (P = 0.003), and subgroups 2 and 3 (P = 0.042) with respect to overall survival was observed (Table 5).

Analysis of the prognosis in different subgroups showed that the median OS in the high pre- and post-treatment ALI subgroup (group 4) was the highest (64.67 months, P < 0.0125), while the prognosis of patients were poorer in the low pre- and post- treatment ALI subgroup (median OS: 32.23 months, P < 0.0125), as well as high in the pre-treatment but low in the post-treatment ALI subgroup (median OS: 33.31 months, P < 0.0125). The median OS in the patients that the post-treatment ALI increased was better than the ones with high pre-treatment but low post-treatment ALI (subgroup 2 vs. subgroup 3: 56.78 vs. 33.31 months, P < 0.0125). In addition, for the patients with low pre-operative ALI, the median OS in the ones that the ALI increased after 4 courses treatments (subgroup 2) was better (subgroup 1 vs. subgroup 2: 32.23 vs. 56.78 months, P < 0.0125) (Figure 3).

Discussion

Multiple myeloma is a heterogeneous disease which is characterized by genomic alterations, which is important in MM risk stratification. In this study, we investigated the prognostic significance of the ALI as a marker for predicting the prognosis of MM. The results of this study showed that ALI score is an independent predictor for MM patients. And, low ALI (≤ 45.8) predicted the poor prognosis of newly diagnosed MM patients compared to patients with high ALI. Low ALI group showed higher risk of β2 microglobulin elevation, more advanced ISS, and TP53 gene mutation. Independent risk factors that influenced the OS of MM patients were ALI, extramedullary infiltration, TP53, Plt, and bone destruction. Similarly, ALI, extramedullary infiltration, TP53, Plt, and complex chromosome karyotype were found to be independent risk factors influencing the PFS of MM patients.

Previous studies have demonstrated that tumor microenvironment plays a significant role in the development, progression, recurrence, and metastasis of tumors. Markers of immunological inflammatory response participate in the inflammatory responses of tumors, and also play important roles in the prognosis of patients (23). The immunological immune responses of tumor and heterogenous tumor clones could promote the release of new immunomodulatory factors from cells of microenvironment, which modulates the tumor microenvironment, and inhibit tumor cell apoptosis, promote angiogenesis, active cell adhesion molecules (CAMs), and damage genetic materials, which in-turn create an immunosuppressive microenvironment favoring the survival of myeloma cells (24). Actual activities of the immune functions and homeostasis in medullar immunological microenvironment in the body are difficult to be measured. To date, for different cancer several inflammatory markers has been reported, like CRP (25), albumin (26), neutrophil-to-lymphocyte ratio (NLR) (27), and platelet-to-lymphocyte ratio (PLR) (28). Recent studies on the effects of NLR on prognosis of MM patients have been reported (22, 23). Elevated NLR has been considered associated with the inflammatory responses of

tumors, promoting the transition of normal cells to tumor cells, form the microenvironment favoring the growth of tumor, and promote the growth, invasion, and metastasis of tumors (22). Higher NLR generally indicates poorer prognosis, so it's taken into consideration in assessing the ALI.

Previous studies have demonstrated that ALI could be associated with the prognosis of patients with some tumors (24). The median OS of lung cancer patients in the low ALI group was significantly lower than the ones with high ALI, and the multivariate analysis showed that ALI was an independent risk factor influencing the lung cancer patients (24). In our study, ALI is known to act as independent risk factor with respect to overall survival and progression free survival in MM patients. Also, the PFS and OS of patients with low ALI were significantly shorter than the ones with high ALI.

Studies have shown that the increase in β2-microglobulin expression levels in serum, relates to the high tumor burden and kidney damage in MM patients, with serum β2-microglobulin was an independent risk factor for OS (5). In our study, low ALI group had a higher risk of β2 microglobulin elevation compared to the high ALI group. Serum β2-microglobulin combined with serum protein level were proved to be the simplest staging index for MM (7). As one of the prognosis predictors of the ISS staging system, which is recommended by the International Prognostic Scoring System (ISS) for MM patients [(7)], low ALI group had more advanced ISS in our study.

In addition, our study also showed that the overall response rate (≥ PR rate) was higher in the high ALI group than low ALI group, but it was not statistically significant. We speculated that this finding could be associated with the relatively small sample size and the retrospective design of the study. In addition, the treatment strategy for the patients were not identical, which could also influence the outcome. More studies are needed further to verify the findings.

ROC curve is generally used for the selection of ALI cut-off value, of which 18, and 47 have already been applied in the studies on lung cancer (12, 15, 24). The ALI cut-off value in this study was 45.8, according to the ROC curve. The findings showed that after 4 courses treatment, the ALI of the low ALI group increased to ≥ 45.8 (subgroup 2), of whom the median OS was significantly higher than the ones that the ALI maintained at low level (subgroup 1), suggesting the treatment increased the survival of patients, and indicated that the immunological microenvironment were restored. Our findings suggested that the increase of ALI during treatment could reflect the recovery of immunological microenvironment, which then substantially improve the prognosis of MM patients. These findings also demonstrated that the overall response rate and OS in patients with low pre-treatment, but high post-treatment ALI (subgroup 2, 56.78 months) were significantly better than the ones with high pre-treatment but low post-treatment ALI (subgroup 3, 33.31 months). These findings indicated that the restoration of immunological microenvironment could be especially important, while low ALI during treatment could be an early marker of poor clinical prognosis. Therefore, more effective treatments, such as VRD regimen or stem cell transplantation, could be selected for the patients in this subgroup.

There were several limitations in this study. First, this was a single-center, retrospective study with relatively low sample size, and thus the study findings could be limited. Second, predicting MM patient prognosis by ALI in early stage involves high requirements. However, for patients with no underlying disease, did not receive chemotherapy, with no immunological disease, and with no evident systemic or local infection, ALI had certain diagnostic values. Also, the study assessed two different stage systems, i.e DS and ISS for a longer timeline, which varied and revised along the years, and this limits the outcome at large. The selection of ALI cut-off value, as well as the association of ALI with the treatment responses and prognosis of MM patients need to be validated in further multi-center, prospective studies with larger sample sizes. The verification of the findings could help us better in conducting the risk stratification of MM patients.

Conclusions

The study concludes that ALI score is an independent predictor for MM patients. Low ALI (≤ 45.8) could predict the poor prognosis of newly diagnosed MM patients. The dynamic changes of ALI during chemotherapy have certain value in predicting the prognosis, especially for MM patients with low pre-treatment ALI. So, we propose ALI as a low-cost and convenient inflammatory marker that could predict the prognosis of MM patients, which could not only be a supplement for the commonly used prognostic indicators, but also seemed to have more profound significance. Need more studies to further validate the value of ALI in predicting the prognosis in larger group of MM patients received different treatments.

Abbreviations

ALI: Advanced lung cancer inflammation index; MM: multiple myeloma; ROC: receiver operating characteristic; OS: overall survival; PFS: progression-free survival; ASCT: autologous stem cell transplantation; ISS: International Staging System; R-ISS: Revised-International Staging System; D-S: Durie-Salmon; IMWG: International Myeloma Working Group; mSMART: Mayo Stratification of Myeloma and Risk-Adapted Therapy; NSCLC: non-small-cell lung cancer; BMI: body mass index; ALB: albumin; NLR: neutrophil to lymphocyte ratio; mALI: modified ALI; NLR: neutrophil/lymphocyte ratio; Hb: hemoglobin; PLt: platelet count; β2MG: β2 microglobulin; Cr: creatinine; LDH: lactic dehydrogenase; EMD: extramedullary infiltration; Ca: calcium; FISH: fluorescence *in situ* hybridization; CAMs: cell adhesion molecules; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL28913). All methods were carried out in accordance with the Declaration of Helsinki and guidelines of the Ethics Committee.

Informed consents were waived by the Ethics Committee of the Affiliated Hospital of Qingdao University due to the inherent obstacle of retrospective analysis.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Junxia Huang and Juanjuan Hu contributed to design, analysis of data, drafted and critically revised the manuscript. Yan Gao and Fanjun Meng participated in conception, and drafted the manuscript. Tianlan Li, Chuanxia Mao, Shanshan Liu, Xue Shi and Wei Wang helped to analyze data, and critically revised the manuscript. Xianqi Feng contributed to conception, design, analysis of data, drafted and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Hanbali A, Hassanein M, Rasheed W, Aljurf M, Alsharif F. The Evolution of Prognostic Factors in Multiple Myeloma. Adv Hematol. 2017;2017:4812637.
2. Healy CF, Murray JG, Eustace SJ, Madewell J, O'Gorman PJ, O'Sullivan P. Multiple myeloma: a review of imaging features and radiological techniques. Bone Marrow Res. 2011;2011:583439.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
4. Liu J, Liu W, Mi L, Zeng X, Cai C, Ma J, et al. Incidence and mortality of multiple myeloma in China, 2006–2016: an analysis of the Global Burden of Disease Study 2016. J Hematol Oncol. 2019;12:136.

5. Zhang Y, Chen XL, Chen WM, Zhou HB. Prognostic Nomogram for the Overall Survival of Patients with Newly Diagnosed Multiple Myeloma. Biomed Res Int. 2019;2019:5652935.
6. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer. 1975;36:842–54.
7. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol. 2005;23:3412–20.
8. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33:2863–9.
9. Filonzi G, Mancuso K, Zamagni E, Nanni C, Spinnato P, Cavo M, et al. A Comparison of Different Staging Systems for Multiple Myeloma: Can the MRI Pattern Play a Prognostic Role? AJR Am J Roentgenol. 2017;209:152–8.
10. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23:3–9.
11. Kumar SK, Mikhael JR, Buadi FK, Dingli D, Dispenzieri A, Fonseca R, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc. 2009;84:1095 – 110.
12. Jafri SH, Shi R, Mills G. Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review. BMC Cancer. 2013;13:158.
13. Zhang Y, Chen B. Prognostic Value of the Advanced Lung Cancer Inflammation Index in Patients with Lung Cancer: A Meta-Analysis. Dis Markers. 2019;2019:2513026.
14. Kim JH, Oh SY, Kang JH, Kang MH, Ji JH. The prognostic significance of the advanced lung cancer inflammation index(ALI) in patients with advanced biliary tract cancer: A retrospective study. J Clin Oncol. 2020;38:e16613-e.
15. Shiroyama T, Suzuki H, Tamiya M, Tamiya A, Tanaka A, Okamoto N, et al. Pretreatment advanced lung cancer inflammation index (ALI) for predicting early progression in nivolumab-treated patients with advanced non-small cell lung cancer. Cancer Med. 2018;7:13–20.
16. Kim EY, Kim N, Kim YS, Seo JY, Park I, Ahn HK, et al. Prognostic Significance of Modified Advanced Lung Cancer Inflammation Index (ALI) in Patients with Small Cell Lung Cancer_ Comparison with Original ALI. PLoS One. 2016;11:e0164056.
17. Di Marzo L, Desantis V, Solimando AG, Ruggieri S, Annese T, Nico B, et al. Microenvironment drug resistance in multiple myeloma: emerging new players. Oncotarget. 2016;7:60698–711.
18. Romano A, Parrinello NL, Consoli ML, Marchionni L, Forte S, Conticello C, et al. Neutrophil to lymphocyte ratio (NLR) improves the risk assessment of ISS staging in newly diagnosed MM patients treated upfront with novel agents. Ann Hematol. 2015;94:1875–83.

19. Kelkitli E, Atay H, Cilingir F, Güler N, Terzi Y, Ozatlı D, et al. Predicting survival for multiple myeloma patients using baseline neutrophil/lymphocyte ratio. Ann Hematol. 2014;93:841–6.
20. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-48.
21. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17:e328-e46.
22. Ishizuka M, Oyama Y, Abe A, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients undergoing surgery for gastric cancer. J Surg Oncol. 2014;110:935–41.
23. Troppan K, Deutsch A, Gerger A, Stojakovic T, Beham-Schmid C, Wenzl K, et al. The derived neutrophil to lymphocyte ratio is an independent prognostic factor in patients with diffuse large B-cell lymphoma. Br J Cancer. 2014;110:369–74.
24. Shi L, Qin X, Wang H, Xia Y, Li Y, Chen X, et al. Elevated neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio and decreased platelet-to-lymphocyte ratio are associated with poor prognosis in multiple myeloma. Oncotarget. 2017;8:18792–801.
25. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
26. André T, Najar M, Stamatopoulos B, Pieters K, Pradier O, Bron D, et al. Immune impairments in multiple myeloma bone marrow mesenchymal stromal cells. Cancer Immunol Immunother. 2015;64:213–24.
27. Khandavilli SD, Ceallaigh PO, Lloyd CJ, Whitaker R. Serum C-reactive protein as a prognostic indicator in patients with oral squamous cell carcinoma. Oral Oncol. 2009;45:912–4.
28. Tolia M, Tsoukalas N, Kyrgias G, Mosa E, Maras A, Kokakis I, et al. Prognostic Significance of Serum Inflammatory Response Markers in Newly Diagnosed Non-Small Cell Lung Cancer before Chemoirradiation. Biomed Res Int. 2015;2015:485732.

Tables

Table 1. Relationship between ALI and Cytogenetics by FISH in patients with MM

		Total	ALI≤45.8	ALI45.8	P
IgH	Positive	68 (54.8%)	30 (48.4%)	26 (41.9%)	0.470
	Negative	56 (45.2%)	32 (51.6%)	36 (58.1%)	
TP53	Positive	16 (12.9%)	12 (19.4%)	4 (6.5%)	0.032
	Negative	108 (87.1%)	50 (80.6%)	58 (93.5%)	
RB-1	Positive	57 (46.0%)	30 (48.4%)	27 (43.5%)	0.589
	Negative	67 (54.0%)	32 (51.6%)	35 (56.5%)	
1Q	Positive	60 (48.4%)	29 (46.8%)	31 (50%)	0.719
	Negative	64 (51.6%)	33 (53.2%)	31 (50%)	

Abbreviations: Tp53, p53 tumor suppressor protein encoding gene; RB-1, Tumor suppressor gene; IgH, immunoglobulin heavy locus; 1Q, 1q chromosome locus; ALI, Advanced lung cancer inflammation index (ALI); FISH, Fluorescence in situ hybridization.

Table 2. Univariate and multivariate analyses of prognostic factors for overall survival of patients with MM

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Male sex	0.773	0.466 - 1.281	0.318			
Age (years)	1.611	1.007 - 2.577	0.047			
Type	1.001	0.765 - 1.309	0.994			
ISS stage	1.577	0.981 - 2.535	0.06			
DS stage	1.762	0.900 - 3.447	0.098			
Other Parameters						
PCs (%)	1.144	0.705 - 1.856	0.585			
Hemoglobin (g/L)	0.692	0.430 - 1.115	0.130			
Platelet count ($x10^9$/L)	0.451	0.273 - 0.747	0.002	0.212	0.072 - 0.626	0.005
Serum Cr (umol/L)	1.21	0.674 - 2.174	0.523			
LDH (U/L)	2.226	1.349 - 3.672	0.002			
EMD	0.273	0.162 - 0.460	<0.001	0.141	0.043 - 0.460	0.001
Bone destruction	1.743	1.070 - 2.839	0.026	4.075	1.202 - 13.807	0.024
High-risk cytogenetics	3.039	1.614 - 5.723	0.001			
ALI	0.522	0.317 - 0.862	0.011	0.145	0.036 - 0.589	0.007
Cytogenetic abnormalities						
IgH	1.598	0.747 - 3.418	0.227			
TP53	0.313	0.145 - 0.674	0.003	0.22	0.062 - 0.786	0.020
RB-1	0.759	0.370 - 1.557	0.453			
1Q	0.633	0.307 - 1.308	0.217			

Abbreviations: DS stage, Durie-Salmon staging system (D-S); IIS stage, The International Staging System (ISS), Tp53, p53 tumor suppressor protein encoding gene; RB-1, Tumor suppressor gene; IgH; 1Q, 1q chromosome locus; Immunoglobulin heavy locus. EMD, Extramedullary infiltration; PCs, Bone marrow plasma cell; PLt, Platelet count; Scr, Serum Creatinine; LDH, lactic dehydrogenase.

Table 3. Univariate and multivariate analyses of prognostic factors for progress free survival of patients with MM

	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Male	0.661	0.399 - 1.093	0.107			
Age (years)	1.631	1.023 - 2.600	0.040			
Type	0.961	0.736 - 1.255	0.770			
ISS stage	1.455	0.909 - 2.326	0.118			
DS stage	1.879	0.962 - 3.673	0.065			
Other Parameters						
PCs (%)	1.424	0.883 - 2.294	0.147			
Hemoglobin (g/L)	0.582	0.363 - 0.932	0.024			
Platelet count ($x10^9$/L)	0.428	0.260 - 0.705	0.001	0.267	0.091 - 0.789	0.017
Serum Cr (umol/L)	1.189	0.671 - 2.107	0.553			
LDH (U/L)	1.769	1.079 - 2.899	0.024			
EMD	0.338	0.203 - 0.562	<0.001	0.161	0.046 - 0.566	0.004
Bone destruction	1.497	0.926 - 2.420	0.100			
High-risk cytogenetics	1.743	1.070 - 2.839	0.026	5.942	1.533 - 23.029	0.010
ALI	0.544	0.333 - 0.891	0.015	0.193	0.061 - 0.608	0.005
Cytogenetic abnormalities						
IgH	1.975	0.920 - 4.242	0.081			
TP53	0.169	0.077 - 0.375	<0.001	0.057	0.014 - 0.231	<0.001
RB-1	0.731	0.357 - 1.500	0.393			
1Q	0.726	0.352 - 1.498	0.386			

Abbreviations: DS stage, Durie-Salmon staging system (D-S); IIS stage, The International Staging System (ISS), Tp53, p53 tumor suppressor protein encoding gene; RB-1, Tumor

suppressor gene; IgH; 1Q, 1q chromosome locus; Immunoglobulin heavy locus. EMD, Extramedullary infiltration; PCs, Bone marrow plasma cell; PLt, Platelet count; Scr, Serum Creatinine; LDH, lactic dehydrogenase.

Table 4. Relationship between ALI subgroup and treatment effect and prognosis of MM patients

ALI subgroups		subgroup1※	subgroup2▲	subgroup3□	subgroup4	P
PR	Yes	76 (68.5%)	27 (96.4%)※	48 (71.6%)▲	43 (79.6%)	0.016
	No	35 (31.5%)	1 (3.6%)	19 (28.4%)	11 (20.4%)	
VGPR	Yes	57 (51.4%)	22 (78.6%)※	31 (46.3%)▲	29 (53.7%)▲	<0.001
	No	54 (48.6%)	6 (21.4%)	36 (53.7%)	25 (46.3%)	
Median PFS (months)		25.01	48.60※	29.29▲	38.44※	0.000
Median OS (months)		32.23	56.78※	33.31▲	64.67※	0.001

Note: ※P□0.0083 vs subgroup1; ▲P□0.0083 vs subgroup2; □P□0.0083 vs subgroup3.

Table 5. Comparison of OS and PFS between subgroups

	OS		PFS	
	Chi-square	P	Chi-square	P
Subgroup 1 vs. subgroup 2	10.02	0.002	9.771	0.002
Subgroup 1 vs. subgroup 3	1.567	0.211	3.207	0.073
Subgroup 1 vs. subgroup 4	11.21	0.001	8.661	0.003
Subgroup 2 vs. subgroup 3	5.711	0.017	4.137	0.042
Subgroup 2 vs. subgroup 4	0.392	0.531	0.968	0.325
Subgroup 3 vs. subgroup 4	2.747	0.097	1.858	0.173