Development and Validation of a Prognostic Implications of Chromosome Abnormalities Algorithm for Newly Diagnosed Multiple Myeloma

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Abstract

BACKGROUND: Fluorescence in situ hybridization (FISH) evaluation is essential for initial risk stratification in multiple myeloma (MM). While the presence of specific cytogenetic abnormalities confers a heterogeneity impact on prognosis, the cutoff values are not exactly comparable among different centers, we performed K-Adaptive Partitioning (Kaps), a novel statistical method, to development and validation of a prognostic implications of chromosome abnormalities algorithm for newly diagnosed multiple myeloma

METHODS: A total of 533 patients with newly diagnosed MM admitted to Shanghai Changzheng Hospital were enrolled. All patients underwent FISH detect cytogenetic abnormalities. The prognostic impact of cytogenetic abnormalities (CA) detected by FISH were analyzed.

RESULTS: The K-Adaptive Partitioning method was used to calculate the chromosomal abnormal cut-off values as follows: 17p - 20.1%, 13q - 85%, 1q21 + 39%, t (11, 14) 55.5%, t (14,16) 87%, t (4,14) 53.5%. According to EMN criteria for CA, 17p- and 1q21 + are the independent factors affecting both OS and PFS among CA. The analysis based on the cutoff value obtained by Kaps suggests that 13q-, t(14,16) , 17p- and 1q21 + are independent factors affecting OS among CA; t(14,16) , 17p- and 1q21 + are independent factors affecting PFS among CA. Based on the survival analysis results, the prognostic model was constructed. The c-index of the prognostic model calculated by the Kaps method was 0.719 (95% CI, 0.683 to 0.756; corrected 0.707), while the c-index of the prognostic model according to the EMN criteria was 0.714 (95% CI, 0.678 to 0.751; corrected 0.696). To analyze the influence of the number of adverse CA on the prognosis, both the EMN criteria and the criteria analysis by the Kaps suggest that the more adverse CA, the OS and PFS became shorter.

CONCLUSION: This study shows that chromosomal abnormalities in different proportions and combinations can affect the prognosis of multiple myeloma patients. Effective criteria should be formulated to evaluate the prognosis of MM patients better.

Background

As a malignant disease of plasma cells, multiple myeloma (MM) had been reported that there were significant differences in the clinical manifestations, prognosis, and response to treatment in MM patients with different cytogenetic abnormalities (CA) (1). The process of MM formation is the process of CA changing accompanying with the clinical characteristics of MM patients changing(2). Recently, fluorescence in situ hybridization (FISH) was a standard method for the characterization and quantification of CA in MM patients. However, the detecting methods and the definition of cutoff value was still controversial. The European Myeloma Network (EMN) criteria recommended that the cutoff value should be 20% for abnormal chromosome numbers, the cutoff level should be 10% for IgH translocations and other translocations. Several scholars recommended that the cutoff value of 17p- was

60%, 1q21+ was 30%, and 13q- was 74% in the IFM 99 test(3), the cutoff value of 1q21+was 20% and 13q- was 10% at the Mayo Center(4).

How to conduct risk stratification of MM patients by FISH results is still controversial, the clinical significance of the proportion of different chromosomal abnormalities detected by FISH is also unclear. Therefore, we conduct this study to investigate the prognostic implications of chromosome abnormalities algorithm for newly diagnosed MM in order to provide a more accurate prediction of the real world according to the OS of actual patients.

Methods

Patients

From January 1, 2008 to December 31, 2015, patients with MM who were treated at Shanghai Changzheng Hospital were recruited in this study. Information about patient at the time of initial diagnosis, including age, gender, DS score, ISS score, hemoglobin (HB), Clonal BM plasma cells, creatinine (Cr), serum calcium (Ca), β2-microglobulin(β2M), albumin (ALB), platelet (PLT), lactate dehydrogenase (LDH), bone marrow plasma cell count, FISH test results, and therapies and response status were abstracted from the patients' hospital records. All patients with MM were eligible for the 2014 IMWG criteria for the diagnosis of MM and were tested for CA by FISH before treatment. All participants were followed up until July 31, 2018. Patients gave written informed consent, which were performed in accordance with the Declaration of Helsinki.

FISH studies

All patients were tested for CA by FISH. The DNA probes included 1q21(CKS1B), 17p-(TP53), 13q-(D13S319), IgH probes, dual fusion probe probes t(4;14)(p16;q32)/FGFR3-IGH, t(11;14)(q13;q32) /CCND1-IGH, t(14;16)(q32;q23) /MAF-IGH, excluded t (14; 20) due to the low proportion among MM patients, other probes were used according to the product instructions. All samples were purified by anti-CD138 magnetic beads of plasma cells before FISH. OPLYMPUS BX51 fluorescence microscope was used to observe the fluorescence hybridization signals of 200 interphase cells in each sample with each probe under the excitation of DAPI/FITC/RED trichrome filter. The image was analyzed by FISH analysis software (Video Test).

The main endpoints

In this study, the primary endpoint was overall survival (OS) which was calculated from the time of diagnosis to the time of death for any cause. The secondary endpoint was progress free survival (PFS), and calculated from the time of diagnosis to the time of progression or any cause of death.

Statistical analysis

SAS Version 9.4 and R version 3.3 were used for statistical analysis. The continuous variables of normal distribution were expressed as mean ± standard deviation, the continuous variables of non-normal distribution were expressed as median (interquartile range [IQR]), the categorical variables were expressed as frequency (percentage[%]). Kaps method was used to calculate the best cut-off value of OS for each CA(5). Survival curves were compared by the Kaplan-Meier method, log-rank test. Cox proportional hazards model was used to estimate the hazard ratio (HR) along with 95% confidence intervals (95% CIs). Cox stepwise regression was used to screen variables related to OS or PFS among multiple factors. A prognostic model was constructed based on multivariate analysis results and was presented as nomogram. The performance of the prediction model was evaluated by calibration curve and Harrell's concordance index(c-index). At the same time, cross validation is used for internal validation and the corrected c-index is calculated. P values were two-sided, the result was statistically significant if $P \leq 0.05$.

Results

Characteristics of patients

A total of 533 patients who were newly diagnosed as MM were included in this study. Among these 533 patients, there were 325 males (60.98%) and 208 females (39.02%). The median age of the patients was 61 years old (range, 23-87 years old). All patients received at least one novel agent, 476 patients (89.31%) contained bortezomib, 103 patients (19.32%) contained lenalidomide, 282 patients (52.91%) contained thalidomide, followed by stem cell transplants if possible. The median follow-up time was 35.79 (0.21-88.88) months. A total of 324 patients (60.8%) survived at the end of follow-up. All features of the patients are detailed in Table 1.

The effect of single CA on survival

According to the EMN criteria, we investigate the single CA aberration on impaction of prognosis at different clone sizes. The results presented that patients harbored 17p-, 13q-, 1q21+ showed shorter OS and patients harbored 17p-, 1q21+ have shorter PFS based on the EMN criteria. Then, we used Kaps to calculate the best cut-off value of OS and the results showed that the best cut-off value of OS were as follows: 17p - 20.1%, 13q - 85%, 1q21 + 39%, t (11, 14) 55.5%, t (14,16) 87%, t (4,14) 53.5%. Based on the cut-off value calculated by Kaps, we also found that patients harbored 17p-, 13q-, 1q21+, t(4;14), t(11;14), t(14;16showed shorter OS and patients harbored 17p-, 13q-, 1q21+, t(11;14), t(14;16have shorter PFS (Figure 1). The details were listed in the Table 2.

In order to identify which of the single CA aberration was really affecting the prognosis of patients, we further performed multivariate analysis of all CA and other possible survival-related parameters by Cox stepwise regression. Firstly, we analyzed the prognostic factors of PFS or OS according to the EMN criteria. The statistically independent predictors of PFS were 1q21+, 17p-, ISS stage, LDH, M-spike, gender, transplantation schemes. The statistically independent predictors of OS were 1q21+, 17p-, age, ISS stage, LDH, DS stage, M-spike. After that, we analyzed the prognostic factors of PFS or OS according to the cut-off value calculated by Kaps and the results showed that the statistically independent predictors of PFS

were 1q21+, 17p-, t(14;16), ISS stage, LDH, isotype, transplantation schemes. The statistically independent predictors of OS were 1q21+, 17p-, t(14;16), 13q-, age, ISS stage, LDH, M-spike . The details were listed in the Table 3 and Table 4.

Prediction model and validation and calibration

In order to further verify whether the criteria calculated by Kaps can predict survival more accurately, we constructed two prognostic models according to the Cox multivariate analysis results of OS based on the two different criteria. We used nomograms to visualize the prediction model (Figure 2). Besides, we used calibration curve and Harrell's concordance index (c-index) to evaluate the performance of the prediction model. The results showed that the c-index (0.719; 95% CI, 0.683 to 0.756; corrected 0.707) for the nomogram established by Kaps method to predict OS was higher than that calculated by the EMN criteria (0.714; 95% CI, 0.678 to 0.751; corrected 0.696). The calibration curve of the two prognostic models was shown in Figure 3.

The impact of adverse CA number on prognosis

Finally, we analyzed the influence of the number of adverse CA on prognosis. According to the result of multivariate analysis which was calculated by the EMN criteria, we found that there were two adverse lesions: 17p-, 1q21+. Then, patients were divided into three groups: no abnormalities (204 patients, 38.27%), one abnormality (296 patients, 55.53%), two abnormalities (33 patients, 6.19%). The results of the univariate Cox regression analysis showed that the OS [HR, 1.984 (95% CI, 1.452-2.709) P < 0.001] and PFS [HR, 1.740 (95% CI, 1.357-2.232), P < 0.001] of one abnormality group and the OS [HR, 2.920(95% CI, 1.715-4.971), P < 0.001] and PFS [HR, 3.046(95%CI, 1.948-4.762)], P < 0.001] of two abnormalities group were shorter than that of the no abnormalities group. The survival curves were shown in Figure 4A and Figure 4B. Multivariate analysis showed that there were two independent prognostic factors associated with PFS in the three groups: one abnormality group [HR, 1.706 (95% CI, 1.313-2.217), P < 0.001], two abnormalities group [HR, 2.811(95% CI, 1.762-4.485)], P < 0.001]. There were also two independent prognostic factors associated with OS: one abnormality group [HR, 1.887 (95% CI, 1.355-2.630) P < 0.001], two abnormalities group [HR, 2.780 (95% CI, 1.566-4.934), P < 0.001].

The result of multivariate analysis showed there were four adverse lesions: 17p-, 1q21+, 13q-, t (14; 16). Then, patients were divided into four groups: no abnormalities (208 patients, 39.02%), one abnormality (228 patients, 42.78%), two abnormalities (86 patients, 16.14%), more than two abnormalities group (11 patients, 2.06%). The results of the univariate Cox regression analysis showed that the OS [HR, 1.595 (95% CI, 1.147-2.219) P=0.006] and PFS [HR,1.426 (95% CI,1.103-1.844), P=0.007] of one abnormality group, the OS [HR, 3.152(95% CI, 2.161-4.597) P<0.001] and PFS [HR, 2.385 (95% CI, 1.722-3.305), P<0.001] of two abnormalities group, the OS [HR, 12.755(95% CI, 6.426-25.318), P<0.001] and PFS [HR, 7.032 (95% CI, 3.720-13.292), P<0.001] of more than two abnormalities group were shorter than that of the no abnormalities group. The survival curves were shown in Figure 4C and Figure 4D. Besides, multivariate analysis showed that there were three independent prognostic factors associated with PFS: one abnormality group [HR, 1.347 (95% CI, 1.029-1.762), P=0.030], two abnormalities group [HR, 2.281

(95% CI, 1.627-3.199), P<0.001], more than two abnormalities group [HR, 7.766 (95% CI, 3.849-15.667), P<0.001]. There were also three independent prognostic factors associated with OS: one abnormality group [HR, 1.501 (95%CI, 1.059-2.128), P=0.023], two abnormalities group [HR, 2.773 (95% CI, 1.864-4.127), P<0.001], more than two abnormalities group [HR, 17.310 (95% CI, 7.972-37.583), P<0.001].

Discussion

The outcomes of this study presented that CA can affect the prognosis of MM patients with different proportions and combinations. According to the clinical data of this study, the cut-off values of CA calculated by Kaps may have clinical significance were as follows: 17p-20.1%, 13q-85%, 1q21+39%, t (14;16) 87%. The more types of adverse reactions of CA, the worse the prognosis of MM patients.

MM has the characteristics of wide heterogeneity in clinical manifestations and prognosis. The intrinsic mechanism may be related to the structural and quantitative changes of many chromosomes and the oncogene and tumor suppressor gene mutation in MM(6). The diversity of the proportion of cells with specific mutations, the loss of gene function caused by some mutations, the differences in mutation sites between different patients, and the constant evolution of myeloma cells make targeted treatment very difficult(7). Therefore, it was very important to predict the prognosis of different MM patients based on the clinical characteristics of MM patients. At present, the prognostic evaluation system for MM included DS stage, ISS stage, R-ISS stage, mSMART stage, etc(8-11). Among them, DS and ISS were not included in the cytogenetic indicators because they were submitted earlier and based on the conventional prognostic factors. With the deepening of the understanding of the disease, 17p-, 1q21 +, t (4; 14), t (14; 16), etc. were found to be prognostic factors(12-14), then R-ISS staging, mSMART staging were submitted, added with cytogenetic factors and to predict the prognosis of MM patients more accurately. FISH was currently the standard method for the characterization and quantification of CA in MM patients. Furthermore, FISH has become an indispensable tool in the course of diagnosis and subsequent personalized treatment.

However, it was still a controversial issue that what was the optimal percentage of abnormal cytology detected by FISH can be considered positive, which may lead to poor prognosis and further treatment(1). The cut-off values of different chromosomes in different centers were different. For example, the cutoff value of 17p- varied from 10% to 60%(15-19). Some scholars have suggested to give an optimal cutoff value, but more accurate cutoff value is needed in clinical practice so as to judge the prognosis sensitively and efficiently. In order to further explore the effect of different percentage and combinations of CA detected by FISH on the prognosis of MM patients, we did not artificially distinguish each chromosomal abnormality like the study by Gang An et al(20), which was artificially defined and may not be able to make the best distinction between continuous variables. FISH was also used to make the Revised International Staging System for Multiple Myeloma(10). This method can analysis based on the actual patient's OS and provided a minimum partition by log-rank test and find a set of optimal cut-off points without establishing the number and scope of groups in advance(5), which can be called a more accurate prediction in the real world.

In the multivariate analysis, t (11,14), t (4,14) was not independent prognostic factors of MM patients ($p>0.05$) no matter the analysis was based on the EMN criteria or based on the cut-off value calculated by Kaps. T(4,14) was considered as a prognostic factor in previous studies(21, 22), while bortezomib seemed to improve its adverse effects(23-25). In this study, among the patients with t(4,14) ≥10%, the treatment contains bortezomib accounted for 89.36%. It seemed that the survival improvement of patients with t (4,14) may be due to the higher use ratio of bortezomib. As an another adverse prognostic factor, t(14,16) was not the prognostic factor of MM patients when univariate and multivariate analysis according to the cut-off value calculated by Kaps(26). This indicated that although t(14,16) has a prognostic disadvantage, the cut-off value of t(14,16) will affect the result of the analysis, and the cut-off value needed to be reset. However, due to the small number of patients in this study, only 10 patients (1.88%) with t (14,16) ≥10%, the sample size was limited and needed to be expanded in the future. T(11,14) causes upregulation of cyclin D1 and has been considered as a favorable or innocuous factor for prognosis, which is consistent with the findings in this study(27). Among all CA of MM, 17p- may be the most important prognostic factor, accounting for 10%-20% of newly diagnosed MM patients, and mostly present in patients with IgH translocation(28). The current primary treatment regimen did not improve the prognosis of patients with 17p-(29). In this study, we calculated the 17p- optimal cut-off value of 20.1% by Kaps and the results showed that 17p- were unfavorable prognostic factors no matter based on univariate analysis or based on multivariate analysis. Because the EMN recommended the cutoff values was relatively conservative. Therefore, 17p- has a great impact on the prognosis of patients and needs special attention in clinical treatment.

Many previous studies have shown that 1q21+ can lead to poor prognosis in patients with MM(1, 3, 30, 31), which was consistent with our findings. In this study, the criteria according to the EMN and the criteria calculated by Kaps both found that 1q21+ was an independent prognostic factor in both univariate and multivariate analysis. Compared with the EMN criteria, univariate analysis showed that HR values of PFS and OS were higher when 39% were taken as cut-off values. Therefore, if 39% were taken as cut-off values, it can more clearly distinguish the effect of 1q21+ on prognosis in this study. Furthermore, with the increase of 1q21+ percentage, the prognosis of patients gradually deteriorates.

Recently Brian A. Walker et al. found that the copy number of CKS1B (1q21) was related to the prognosis of MM patients, and the prognosis of patients with amplification (≥4 copies) of CKS1B (1q21) on the background of International Staging System III was extremely poor(32). This may indicated that with the increase of 1q21+ percentage, the copy number of CKS1B also increase. Therefore, the FISH detection in subsequent studies should be made clear about the changes in the copy number of CKS1B. The effect of 13q- on prognosis was highly controversial. Some studies suggest that 13q- may lead to poor prognosis(33), while other studies suggested that 13q- alone does not worsen the prognosis of MM patients, but 13q- was associated with prognostic factors 17p- and t(4,14) which leads to poor prognosis(15, 34). In this study, we first performed a survival analysis of patients according to the EMN criteria and we found that although there was a statistical difference between OS in 13q-positive and 13q-negative patients in the univariate analysis. However, in the multivariate analysis, 13q- was not the independent prognostic factor. According to the 85% cut-off value calculated by Kaps, it was found that

13q- was an independent prognostic factor no matter based on univariate analysis or multivariate analysis. Because the stepwise regression method was used for multivariate analysis in this study, it can be ruled out that 13q- was related to other factors which indicated that 13q- alone has an adverse effect on prognosis, but only when the percentage of 13q- cells was large. In order to further verify the accuracy of the cut-off values calculated by Kaps, we constructed prognostic models based on the results of multivariate analysis of the two different criteria and visualized the prognostic models by nomogram. The calibration curve and c-index show that both models can accurately predict the prognosis of patients. The c-index (0.719) and internal validation corrected c-index (0.707) of the prognostic model established according to the criteria calculated by Kaps were greater than the c-index (0.714; corrected 0.696 of the prognostic model established according to the EMN standard. It showed the reliability of this study. As far as our center is concerned, 17p - 20.1%, 13q - 85%, 1q21 + 39%, t (14, 16) 87% was more suitable as the cutoff value than the EMN standard.

Finally, we analyzed the effects of adverse CA numbers on prognosis. Both univariate and multivariate analyses based on EMN criteria or criteria calculated by Kaps showed that PFS and OS in patients with greater than or equal to one adverse lesions had statistical difference when compared with no abnormalities group. The fact that the HR values became larger with the greater adverse CA numbers suggested that with the increase of the number of adverse CA, the prognosis of patients with MM gradually deteriorates. Therefore, lymphoma, the “double-hit theory”, can be applied to MM, just like the study by Walker et al.(32), Shah et al.(30) and mSMART 3.0 updated by Mayo Clinic lately.

In summary, this study showed that 17p-, 13q-, 1q21+ and t (14,16) can lead to poor prognosis, and the proportion of adverse CA will also affect the prognosis of MM patients. In particular, the effect of 13q- on prognosis at the lower number of proportion is often not significant, and is often overlooked clinically. As far as this study is concerned, the best cut-off values for 17p-, 13q-, 1q21+, and t (14,16) were 20.1%, 85%, 39%, and 87%, respectively, can better judge the prognosis of MM patients. The number of adverse CA also affects the prognosis of patients. The more adverse CA numbers, the prognosis is worse.

There were several limitations in this study. Firstly, this study was only a retrospective study, not a randomized control trial. Secondly, this study was a single-center trial with a limited sample size. It was still necessary to expand the sample size in collaboration with other centers to study the effects of CA and other factors on the prognosis of MM patients.

Conclusions

Chromosomal abnormalities in different proportions and combinations can affect the prognosis of multiple myeloma patients. Therefore, effective criteria should be formulated to evaluate the prognosis of MM patients better.

Abbreviations

ALB: albumin; ASCT: Autologous hematopoietic stem cell transplantation; alloSCT: Allogeneic stem cell transplantation; β2M: β2-microglobulin; CA: cytogenetic abnormalities; Ca: serum calcium; c-index: Harrell's concordance index; Cr: creatinine; DS stage: Durie-Salmon stage; EMN: the European Myeloma Network; FISH: Fluorescence in situ hybridization; HB: hemoglobin; HR: hazard ratio; IQR: interquartile range; ISS stage: International Staging System stage; Kaps: K-Adaptive Partitioning; LDH: lactate dehydrogenase; MM: multiple myeloma; OS: overall survival; PFS: progress free survival; PLT: platelet; sFLC: serum free light chain

Declarations

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Authors' contributions

T.L, W.Q, and J.L, collected and analyzed the data, and wrote the first draft, and approved the final version of the manuscript; All authors performed patient management and approved the final version of the manuscript; J.L, L.L, H.H, and H.J, performed patients' follow-up, participated in final data analysis and approval of the final version of the manuscript; W.F., and J.H. designed the study, performed patient management, and approved the final version of the manuscript, and; J.D. designed the study, performed patient management, analyzed the data, wrote the first draft, approved the final version of the manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

Ethical statement and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Second Military Medical University (Ethical number: 2016SL019). All participants had signed the informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Tables

Due to technical limitations, table 1,2,3,4 is only available as a download in the Supplemental Files section.

Figures

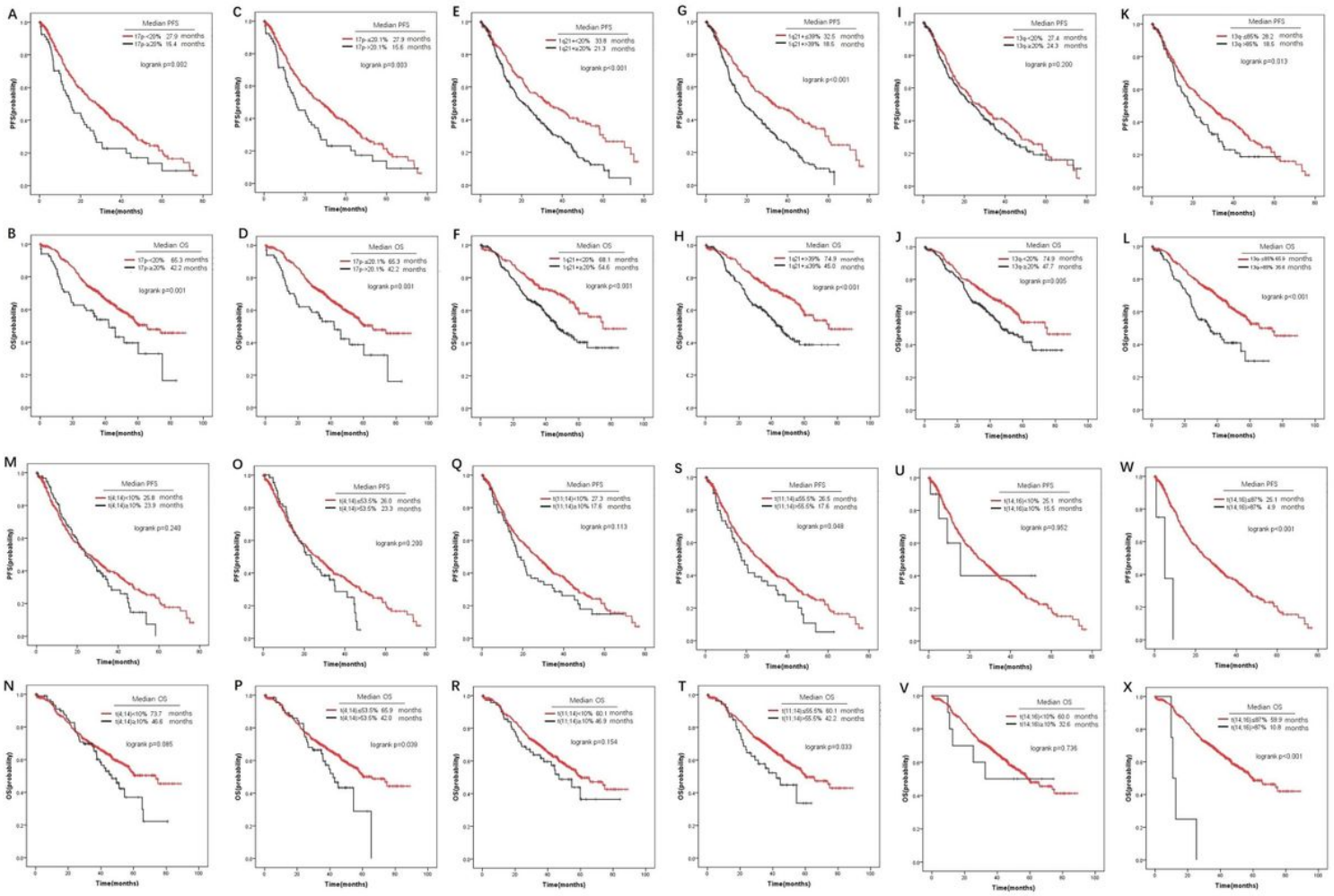

Figure 1

Survival analysis. Survival analysis for patients with 17p-≥20% vs 17p-<20%(A-B), 17p->20.1% vs 17p-≤20.1%(C-D), 13q-≥20% vs 13q-<20%(E-F), 13q->85% vs 13q-≤85%(G-H), 1q21+≥20% vs 1q21+ <20%(I-J), 1q21+ >39% vs 1q21+≤39%(K-L), t(4;14)≥10% vs t(4;14) <10%(M-N), t(4;14) >53.5% vs t(4;14) ≤53.5%(O-P), t(11;14)≥10% vs t(11;14) <10%(Q-R), t(11;14) >55.5% vs t(11;14) ≤55.5%(S-T), t(14;16)≥10% vs t(14;16) <10%(U-V), t(14;16) >87% vs t(14;16) ≤87%(W-X)

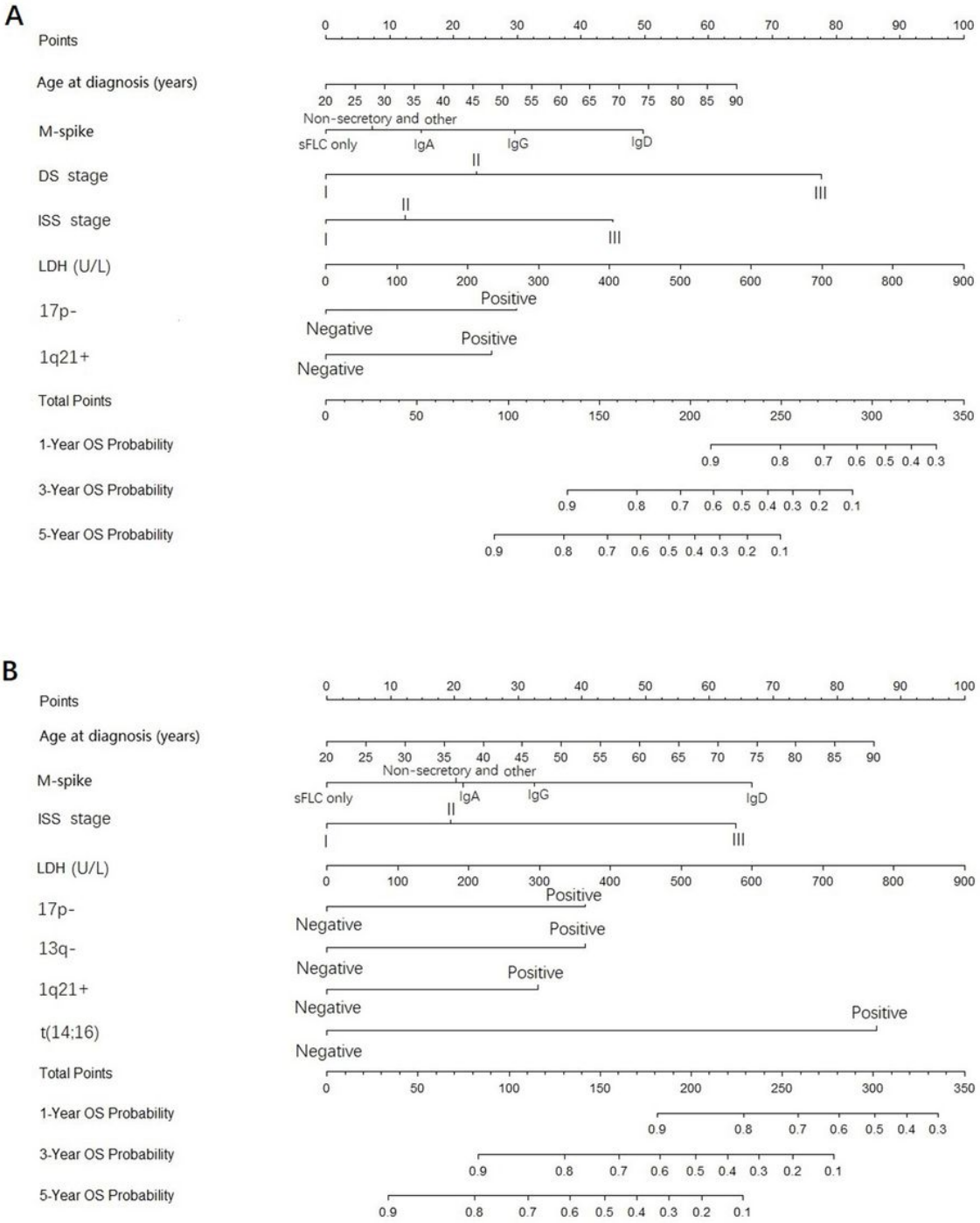

Figure 2

Nomograms analysis. Nomograms based on the EMN criteria predicted 1-, 3-, and 5-year overall survivals in patients with newly diagnosed MM(A), Nomograms based on the cut-off value calculated by Kaps predicted 1-, 3-, and 5-year overall survivals in patients with newly diagnosed MM(B). For each characteristic, find the position on the 0–100 scale at the top and then add these points. Find the number on the “Total Points” scale and then read the OS probabilities at the (1-, 3- and 5-year OS probability) line of the nomogram.

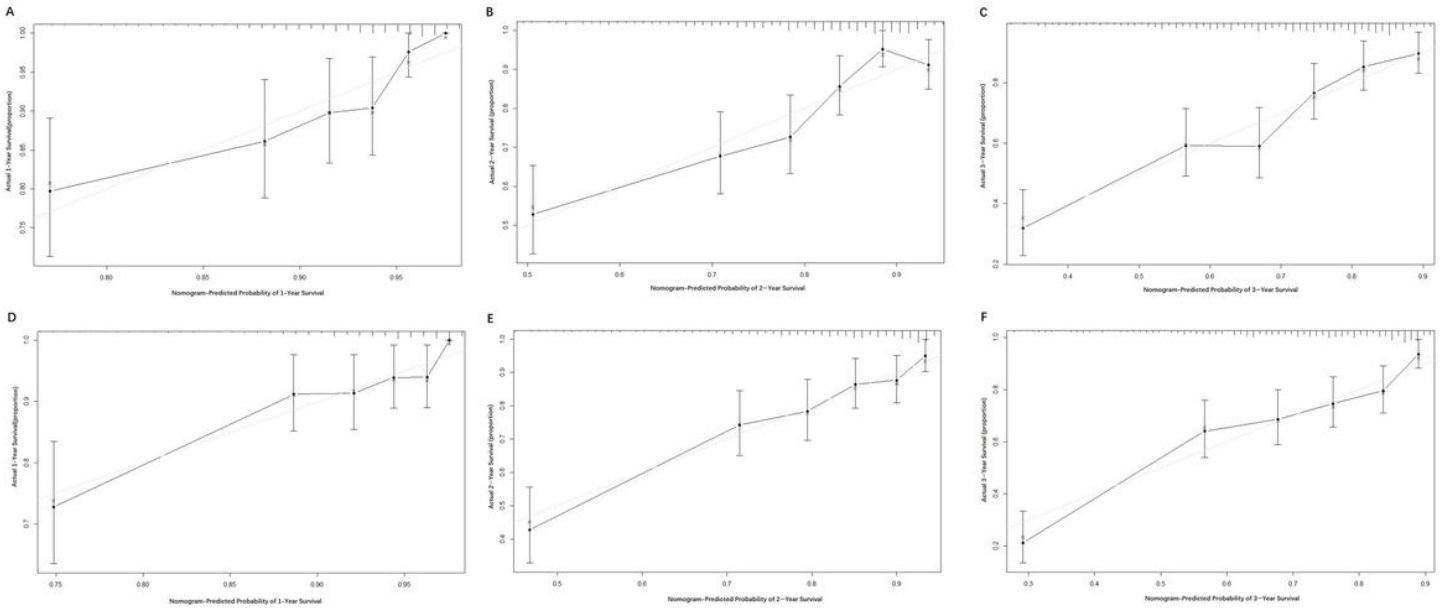

Figure 3

The calibration curves for nomograms. The calibration curves for nomograms calculated by the EMN criteria for patients with MM predicting OS at 1, 2 and 3 year after diagnosis (A-C). The calibration curves for nomograms established by Kaps method for patients with MM predicting OS at 1, 2 and 3 year after diagnosis (D-F).

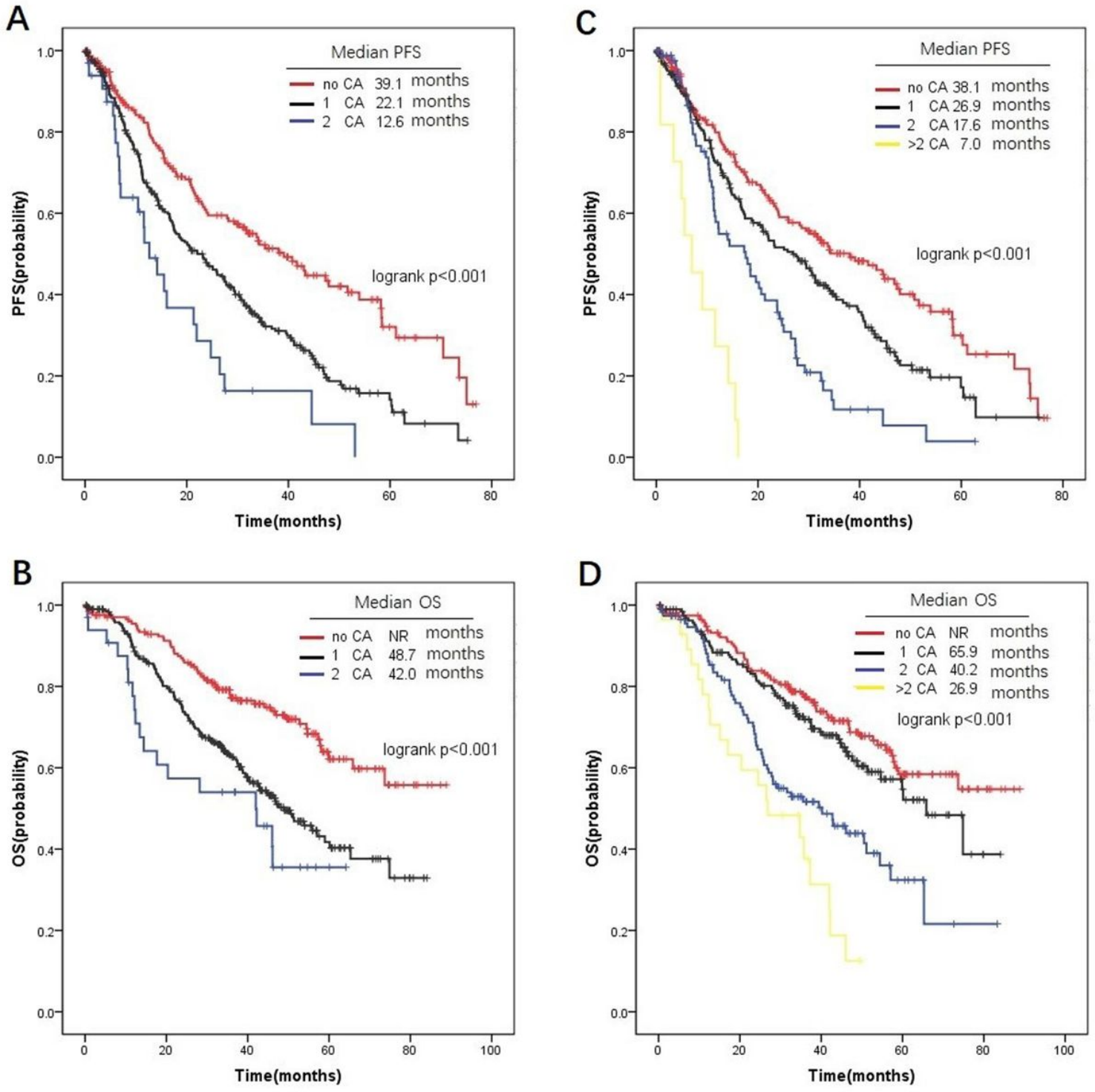

Figure 4

The Impact of adverse CA. Impact of the number of adverse CA according to the EMN criteria (A-B). Impact of the number of adverse CA according to the standard calculated by Kaps(C-D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx