Multiple myeloma gammopathies

Clinical features and survival outcomes in IgD myeloma: a study by Asia Myeloma Network (AMN)

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To the Editor:

Immunoglobulin D (IgD) myeloma is a rare isotype that comprises 1–2% of multiple myeloma (MM) patients [1–3], which has significantly inferior survival for a median overall survival (OS) between 13 and 21 months [4–6].

Given the lack of large cohort with comprehensive clinical and cytogenetic assessment, knowledge about IgD myeloma is obtained mostly from a limited sample size [7]. Therefore, we carried out a multicenter retrospective study to evaluate the prevalence, clinical features, prognosis, and to develop and validate a prognostic model, including 356 patients with IgD myeloma from 14 centers of Asian Myeloma Network (AMN).

Data were collected from China, Korea, and Singapore diagnosed from 2002 to 2019 (Supplementary Table 1). Ethical committee approvals were obtained and study protocol was approved by the Institutional Review Board of each institution. To avoid clinical information leak, and get

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## Table 1

Table 1 Characteristics of the study populations.

| Variable                        | IgD MM (N = 356, %) | Non-IgD MM (N = 712, %) | P value |
|---------------------------------|---------------------|-------------------------|---------|
| Sex                             | Male                | 241 (67.7)              | 429 (60.3) | 0.018 |
|                                 | Female              | 115 (32.3)              | 283 (39.7) | 0.006 |
| Age at diagnosis, years         | Median (range)      | 56 (32–85)              | 62 (23–96) | <0.001 |
|                                 | <65                 | 286 (80.3)              | 468 (65.7) | <0.001 |
|                                 | ≥65                 | 70 (19.7)               | 244 (34.3) | 0.812 |
| DS Stage                        | I                   | 8 (2.2)                 | 16 (2.2) | 0.018 |
|                                 | II                  | 23 (6.5)                | 54 (7.6) | 0.006 |
|                                 | III                 | 323 (91.3)              | 642 (90.2) | 0.006 |
| ISS stage                       | I                   | 70 (19.7)               | 179 (25.1) | <0.001 |
|                                 | II                  | 64 (17.9)               | 262 (36.8) | 0.006 |
|                                 | III                 | 222 (62.4)              | 271 (38.1) | 0.006 |
| Plasma cells of BM (%)          | ≥50                 | 149 (41.9)              | 143 (20.1) | <0.001 |
|                                 | <50                 | 207 (58.1)              | 569 (79.9) | 0.006 |
| Hemoglobin level (g/L)          | <100                | 231 (64.9)              | 420 (59) | 0.063 |
|                                 | ≥100                | 125 (35.1)              | 292 (41) | 0.006 |
| Platelet count (10^9/L)         | <100                | 76 (22.3)               | 91 (12.8) | <0.001 |
|                                 | ≥100                | 280 (78.7)              | 621 (87.2) | 0.006 |
| Serum LDH (U/L)                 | ≥245                | 136 (38.2)              | 177 (24.9) | <0.001 |
|                                 | <245                | 220 (61.8)              | 535 (75.1) | 0.006 |
| Serum creatinine level (mg/dL)  | ≥2                  | 137 (38.5)              | 131 (18.4) | <0.001 |
|                                 | <2                  | 219 (61.5)              | 581 (81.6) | 0.006 |
| Serum calcium level (mmol/L)    | ≥2.65               | 85 (23.9)               | 105 (14.7) | <0.001 |
|                                 | <2.65               | 271 (76.1)              | 607 (85.3) | 0.006 |
| Light chain restriction         | Kappa               | 40 (11.2)               | 407 (57.2) | <0.001 |
|                                 | Lambda              | 316 (88.8)              | 305 (42.8) | 0.006 |
| Extramedullary plasmacytoma     | Yes                 | 68 (19.1)               | 106 (14.9) | 0.079 |
|                                 | No                  | 288 (80.9)              | 606 (85.1) | 0.006 |
| R-ISS stage                     | I                   | 42 (11.8)               | 114 (16) | <0.001 |
|                                 | II                  | 175 (49.2)              | 449 (63.1) | 0.006 |
|                                 | III                 | 115 (32.3)              | 149 (20.9) | 0.006 |
|                                 | Data missing        | 24 (6.7)               | 0 (0) | 0.006 |
| FLCR                            | 0.01–100            | 137 (38.5)              | 356 (50) | 0.099 |

**Table 1 (continued)**

| Variable                        | IgD MM (N = 356, %) | Non-IgD MM (N = 712, %) | P value |
|---------------------------------|---------------------|-------------------------|---------|
|                                 | ≥0.01, ≥100         | 138 (38.8)              | 356 (50) | 0.006 |
|                                 | Data missing        | 81 (22.7)               | 0 (0) | 0.006 |
| Del (13q) in FISH               | Yes                 | 77 (21.7)               | 261 (36.7) | 0.001 |
|                                 | No                  | 224 (62.9)              | 451 (63.3) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| Del (17p) in FISH               | Yes                 | 35 (9.9)                | 75 (10.5) | 0.006 |
|                                 | No                  | 266 (74.7)              | 637 (89.5) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| Ig21 gains in FISH              | Yes                 | 91 (25.6)               | 368 (51.7) | <0.001 |
|                                 | No                  | 179 (50.2)              | 344 (48.3) | 0.006 |
|                                 | Data missing        | 86 (24.2)               | 0 (0) | 0.006 |
| t (11;14) in FISH               | Yes                 | 88 (24.7)               | 96 (13.5) | <0.001 |
|                                 | No                  | 213 (59.9)              | 616 (86.5) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| t (4;14) in FISH                | Yes                 | 4 (1.1)                 | 136 (19.1) | <0.001 |
|                                 | No                  | 297 (83.5)              | 576 (80.9) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| iq21 gains in FISH              | Yes                 | 20 (5.6)                | 116 (16.3) | <0.001 |
|                                 | No                  | 251 (70.5)              | 596 (83.7) | 0.006 |
|                                 | Data missing        | 85 (23.9)               | 0 (0) | 0.006 |
| t (11;14) and Del (13q) in FISH | Yes                 | 28 (7.9)                | 28 (3.9) | 0.006 |
|                                 | No                  | 273 (76.7)              | 684 (96.1) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| t (11;14) and Del (17p) in FISH | Yes                 | 10 (2.8)                | 5 (0.7) | 0.006 |
|                                 | No                  | 291 (81.8)              | 707 (99.3) | 0.006 |
|                                 | Data missing        | 55 (15.4)               | 0 (0) | 0.006 |
| t (11;14) and 1q21 gains in FISH| Yes                 | 27 (7.6)                | 39 (5.5) | 0.012 |
|                                 | No                  | 243 (68.2)              | 673 (94.5) | 0.006 |
|                                 | Data missing        | 86 (24.2)               | 0 (0) | 0.006 |
Table 1 (continued)

| Variable                     | IgD MM (N = 356, %) | Non-IgD MM (N = 712, %) | P value |
|------------------------------|---------------------|-------------------------|---------|
| t (11;14) and t (4;14) in FISH |                      |                         |         |
| Yes                          | 1 (0.3)             | 0 (0)                   | 0.124   |
| No                           | 300 (84.3)          | 712 (100)               |         |
| Data missing                 | 55 (15.4)           | 0 (0)                   |         |
| t (11;14) and t (14;16) in FISH |                      |                         |         |
| Yes                          | 0 (0)               | 0 (0)                   | NA      |
| No                           | 301 (84.6)          | 712 (100)               |         |
| Data missing                 | 55 (15.4)           | 0 (0)                   |         |
| t (11;14) and double hit in FISH |                      |                         |         |
| Yes                          | 6 (1.7)             | 2 (0.3)                 | 0.003   |
| No                           | 265 (74.4)          | 710 (99.7)              |         |
| Data missing                 | 85 (23.9)           | 0 (0)                   |         |
| t (11;14) and triple hit in FISH |                      |                         |         |
| Yes                          | 0 (0)               | 0 (0)                   | NA      |
| No                           | 270 (75.8)          | 712 (100)               |         |
| Data missing                 | 86 (24.2)           | 0 (0)                   |         |

MM multiple myeloma, Ig immunoglobulin, DS Durie Salmon, ISS international staging system, R-ISS revised ISS, LDH Lactate dehydrogenase, BM bone marrow, FISH fluorescence in situ hybridization, Del deletion, FLCR free light chains ratio, NA not available.

*aThe cooccurrence of any 2 of the following: t(4;14), t(14;16), gain (1q), del(17p).

*bThe cooccurrence of 3 or more of the following: t(4;14), t(14;16), gain(1q), del(17p).

a real sense of the accurate model’s outcomes, we split existing 356 IgD MM to three parts, namely training cohort (one center from Shanghai, n = 212), validation cohort 1 (two centers from Beijing, n = 81), and validation cohort 2 (centers from Korea and Singapore, n = 63). The Least Absolute Shrinkage and Selector Operation (LASSO) Cox regression model to determine prognostic factors from the variables with P < 0.05 in the log-rank tests was performed as described [8, 9]. The quality of the prediction model was measured using the concordance index (C-index) and areas under the time-dependent receiver-operating characteristics (ROC) curves (AUCs). A bootstrap with 1000 re-samples was used for internal validation. SAS 9.4 and R 3.5.1 were used for the statistical analysis.

A total of 356 patients with IgD myeloma represented 2–8.8% of all myeloma patients, especially over 5% IgD myeloma prevalence in Chinese centers. We compared the clinical characteristics of IgD myeloma with 712 (1:2) non-IgD myeloma patients random selected as control matched for year of diagnosis and systemic therapy from Shanghai Changzheng Hospital. Baseline characteristics of total cohort are listed on Table 1 and different centers are shown in Supplementary Table 2. IgD myeloma patients had a higher frequency in male, younger than 65 years, advanced R-ISS stage III, hypercalcemia, elevated creatinine levels, and elevated LDH. Cytogenetic information was available for 301 patients (84.6%), while the 1q21 probe was only performed in 75.8% patients. Notably, 29.2% frequency of t(11;14) was predominantly higher compared to those in non-IgD subtypes (P < 0.001). Among the 88 IgD patients harbored t(11;14), the most frequent chromosome abnormalities (CA) coupled with t(11;14) were 13q- (31.8%), 1q21 + (30.7%), and followed 17p- (11.4%). ‘Double-hit’ or ‘triple-hit’ [10, 11] only occurred 5.6% and 0.3% patients, respectively.

And then, we compared IgD myeloma patients with IgG, IgA, and light chain patients random selected as matched control (Supplementary Table 3). The median age was younger in IgD compared with others myeloma subtypes. Notably, the frequency of t(11;14) was significantly higher than non-IgD subtypes (IgD 29.2% vs IgG 10.6% vs IgA 8.4%, P < 0.001), but was a slight higher than light chain subtype (29.2 vs 24.9%). ‘Double-hit’ phenotype was significant lower in IgD myelomas than others subtypes.

Frontline treatment modalities used are shown in Supplementary Table 4. The overall response rate (ORR) was 88.8%, and very good partial response or better was 58.6% (Supplementary Table 5). After a median follow-up of 8.2, 7.3, and 4.9 years for the three cohorts, the median OS were 36.5 months for the total cohort and 31.2 months in training cohort, 52.2 months in validation cohort 1, and 45.7 months in validation cohort 2 (Supplementary Fig. 1 and Supplementary Table 6). Patients received IMiDs showed a relatively longer median OS than others regimens, however, which untranslated into a significant survival benefit (P = 0.17, Supplementary Fig. 2a), and might be the subgroups limitation. Patients received ASCT had a median OS of 45.7 months, which was a slightly longer than 35 months for non-ASCT patients (P = 0.4, Supplementary Fig. 2b). We subsequently investigated whether cytogenetic aberration was a prognostic factor [12], which showed that CA did not have an impact on OS, suggesting other molecular events overcame initial CA risk features and impact prognosis.

Subsequently, the LASSO Cox regression model to determine prognostic factors from the univariate analysis was performed (Supplementary Table 7). Five clinical parameters with statistically relevant, including lambda light chain, plasma cells in BM >50%, hemoglobin <100 g/L, LDH >245 U/L, and extramedullary plasmacytoma, were integrated into multivariate LASSO regression model (Supplementary Table 8). A nomogram was developed and the risk score was computed as follows: 0.9215 × lambda light chain + 0.6376 × plasma cells in BM (≥50%) + 0.5203 × anemia (<100 g/L) + 0.6864 × LDH (≥245 U/L) + 0.4484 × extramedullary plasmacytoma (variable present = 1, absent = 0, Fig. 1a, b). The predictive accuracy for OS calculated using the C-index was 0.705 (95% CI, 0.663–0.747). In the internal
validation, the corrected C-index of OS was 0.696. Similarly, the C-index for OS in validation cohort 1 was 0.690 (95% CI, 0.612–0.768) and 0.703 (95% CI, 0.608–0.798) in validation cohort 2. The calibration curves of the alternative nomogram to predict the 3-year OS presented in Fig. 1c–e suggested a good fit for the observed nomogram, when compared with the ideal nomogram. The panel displayed an AUC value at 1-year, 3-year, and 5-year OS, and the validation sets had a similar high AUC values at these timepoints (Fig. 1f–h).

On the basis of the distribution of the risk scores and the 3-year survival probability, two categories of risk were created with the cut-off point at 1.56: standard risk (risk score ≤ 1.56, n = 156) and high-risk subgroup (risk score > 1.56, n = 200). The clinical characteristics between derivations were presented in Supplementary Table 6. Patients with IgD myeloma at standard risk were significantly better than high-risk subgroup (Fig. 1i). Similar results were obtained in training and validation cohorts respectively (Fig. 1j–l). Notably we
identified that ASCT showed a survival advantage in high-risk group, while it did not improve the survival in standard risk group (Supplementary Fig. 3). Moreover the prediction value of the model was independent of induction modalities. This risk model improves the classification of IgD myeloma and may facilitate the development of risk-adapted treatment strategies.

In conclusion, we described the clinical features of 356 IgD myeloma patients, as well as developed and validated a predictive model containing five baseline clinical variables that could group the IgD patients into standard risk and high risk. Meanwhile, we demonstrated that IMiDs therapy might be a trend to benefit for the patient’s outcome, and ASCT could benefit patient with high risk within the predictive model. These findings may provide guidance for management of IgD myeloma and better prognostic stratification for development of risk-adapted treatment strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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