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The usefulness of mutational data on prognosis of myelodysplastic syndromes: alone or incorporated into the IPSS-R?

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Z.J.X. designed the research, was the principal investigator, and took primary responsibility for the paper; B.L. acquired the data, analysed and interpreted the data, and drafted the article; Z.S. performed statistical analysis; J.Q.L., Z.X.S. and H.J.H. acquired clinical data; Z.F.X., T.J.Q., L.W.F., H.L.Z, L.J.P., N.B.H., S.Q.Q., Y.Z. and Z.J.X. recruited the patients; Z.J.X. and G.H. prepared the manuscript.

Conflict-of-Interest disclosure

The authors declare no competing financial interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplemental methods.

Figure S1. Distribution (%) of MDS patients who previously had been categorized by IPSS-R now categorized by Nazha et al model.

Keywords

gene mutation; prognostic model; myelodysplastic syndrome

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal haematopoietic neoplasms with a variable propensity to progress to acute myeloid leukaemia (AML). This emphasises the need to differentiate MDS patients as low or high risk for progression, so that therapy is tailored according to the risk group. Several prognostic models combining traditional morphological and clinical criteria have been developed as default staging systems to risk-stratify patients with MDS, including the International Prognostic Scoring System (IPSS) (Greenberg *et al*, 1997), the World Health Organization (WHO) classification-based Prognostic Scoring System (WPSS) (Malcovati *et al*, 2007), the MD Anderson Prognostic Scoring System (Kantarjian *et al*, 2008) and the revised IPSS (IPSS-R) (Greenberg *et al*, 2012). The IPSS-R, based on large international databases of more than 7000 patients and integrated detailed disease-related and patient-related factors, has been proved as an excellent predictor of MDS prognosis and is most commonly used.

Over the past decade, a MDS-associated gene mutation profile has been confirmed by several large studies (Papaemmanuil *et al*, 2013; Haferlach *et al*, 2014; Makishima *et al*, 2017), ascertaining that some somatic mutations in certain genes could predict patient outcomes (Papaemmanuil *et al*, 2013; Haferlach *et al*, 2014; Makishima *et al*, 2017). For example, *TP53*, *EZH2*, *ETV6*, *RUNX1*, *ASXL1* and *SRSF2* mutations predict poor outcomes, whereas *SF3B1* mutations are associated with better clinical outcomes. However, because of the various combinations of different gene mutations in different patients and overlap between some clinical parameters and gene mutations, there is no consensus about how to use these genetic data in the prognostic scoring systems (Haferlach *et al*, 2014; Gerstung *et al*, 2015).

Recently, Makishima *et al* (2017) developed a prognostic model that was based only on genetic data (type-1 mutation: *FLT3*, *PTPN11*, *WT1*, *IDH1*, *NPM1*, *IDH2* and *NRAS*; type-2 mutation: *GATA2*, *KRAS*, *TP53*, *RUNX1*, *STAG2*, *ASXL1*, *ZRSR2* and *TET2*; *SF3B1*) according to the clonal evolution in MDS. Four risk groups were identified: low (Group III, who had *SF3B1* mutation with no type-1 or type-2 mutations), intermediate-1 (Group IV, with no type-1, type-2 or *SF3B1* mutations), intermediate-2 (Group II, who had type-2 mutations but lacked type-1 mutations) and high (Group I, with type-1 mutations) with significantly different overall survival (OS). Nazha *et al* (2016) developed a novel dynamic prognostic model that combined mutation of *EZH2*, *SF3B1* and *TP53*, IPSS-R score and age to predict OS in patients with MDS. By using this model, four risk groups were identified: low, intermediate-1, intermediate-2 and high with a median OS of 37·4, 23·2, 19·9 and 12·2 months, respectively. In this study, we applied these two novel prognostic models to an independent group of 457 patients with MDS in order to validate the models and compared the OS predictive values of these two models and IPSS-R.

One hundred and twelve genes were detected by targeted sequencing in 457 successive MDS patients who had evaluable karyotypes and had been reclassified according to the 2016 revised WHO criteria (Arber *et al*, 2016). Details about targeted gene sequencing are

described in the Data S1. All patients provided informed consent in compliance with the Declaration of Helsinki. The cohort comprised 277 (61%) males and 180 (39%) females, with a median age of 52 years (range, 14–83 years) (Table I). Two hundred and twenty-six patients (49%) received immune suppressive drugs including ciclosporin and thalidomide. Fifteen patients (3%) received anti-cancer therapy(ies) including aclacinomycin or homo-harringtonine combined with cytarabine and granulocyte-colony stimulating factor (G-CSF; termed CAG or HAG), idarubicin or daunorubicin combined with cytarabine (IA or DA) or melphalan. Seventy-eight patients (17%) received erythropoietin with or without G-CSF, red blood cell and/or platelet transfusions and/or iron chelation with desferrioxamine. Fifty-eight patients (13%) received decitabine, 34 (7%) an allotransplant and 46 (10%) traditional Chinese medicines. Follow-up data was available for 429 (94%) patients. Median follow-up for survivors was 20 months (range, 1–144). Survival distributions were estimated by the Kaplan–Meier method. Cox regression model and the likelihood ratio test were used to evaluate the predictive power. $P < 0{\cdot}05$ were considered statistically significant.

According to the IPSS-R, the risk for 12 (3%) patients was very low, 115 (25%) patients were low, 152 (33%) were intermediate, 92 (20%) were high and 86 patients (19%) were very high risk, with a 5-year OS of 90·9%, 88·1%, 74·5%, 39·8% and 20·1%, respectively ($P < 0{\cdot}001$, Fig 1A). Based on the Makishima model (Makishima *et al*, 2017), 27 patients (6%) were low risk, 263 (58%) were intermediate-1, 121 (27%) were intermediate-2 and 46 (10%) patients were high risk, with a 5-year OS of 80·2%, 71·8%, 55·5% and 35%, respectively ($P = 0{\cdot}003$, Fig 1B). The Nazha model (Nazha *et al*, 2016) classified 131 patients (29%) as low risk, 165 (36%) as intermediate-1, 117 (26%) as intermediate-2 and 44 (10%) as high risk, with a 5-year OS of 88·1%, 68%, 47% and 16·5%, respectively ($P < 0{\cdot}001$, Fig 1C). When comparing the prognostic value of these three prognostic scoring systems using the Cox regression model and the likelihood ratio test, a significantly higher predictive power for OS became evident for the Nazha scoring system, compared with the IPSS-R and Makishima model (2 log-likelihood ratios of Nazha model: 989; IPSS-R: 1012; Makishima model: 1258; Nazha model vs. IPSS-R: $P = 0{\cdot}044$; Nazha model vs. Makishima model: $P < 0{\cdot}001$).

Comparing the IPSS-R with the Nazha model, 12% of patients in the IPSS-R lower risk group (low/very low) were shifted into the higher risk intermediate-2 category in the Nazha model) and 19% of patients in the IPSS-R intermediate risk groupwere shifted into higher risk (intermediate-2). Meanwhile, 7% of the IPSS-R higher-risk (high/very high) patients were down staged into low-risk categories by the Nazha model. Detailed information is shown in Figure S1.

In our study, the utility of the Makishima and Nazha models was confirmed in a cohort of 457 patients with clinical and molecular data available. Moreover, the Nazha model showed higher predictive value than both the IPSS-R and Makishima model. Furthermore, our data indicated that over 10% of patients in the IPSS-R lower risk (very low/low) were reclassified as intermediate-2 risk using the Nazha model. Our data demonstrated that the Nazha model could help clinicians to more precisely define the probability of poor outcome in the lower MDS risk groups, which represent the majority of MDS patients, in whom new approaches, including allogeneic stem-cell transplantation, should be addressed.

In conclusion, a prognostic model that includes clinical and common mutational data can more precisely predict survival in MDS, and the confirmation and revision of novel molecular-clinical scoring systems should continue under international collaboration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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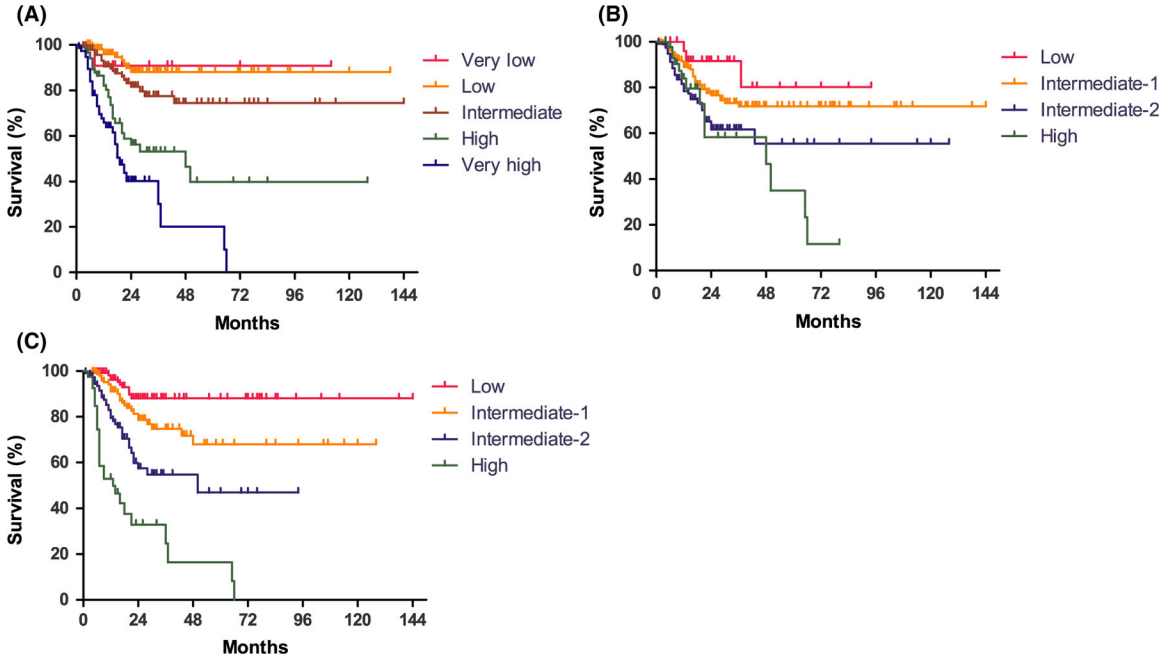

Fig 1.

The overall survival was significantly different in myelodysplastic syndromes (MDS) patients classified according to the (A) Revised International Prognostic Scoring System (IPSS-R; Greenberg *et al*, 2012), (B) Makishima model (Makishima *et al*, 2017) and (C) Nazha model (Nazha *et al*, 2016) as shown by the Kaplan–Meier method.

Table I.

Clinical characteristics of 457 patients with myelodysplastic syndromes.

Patients (*n*)		%
Age, years, Median (range)	52 (14–83)	
Male	277	61
WHO subtype		
MDS-SLD	15	3
MDS-RS-SLD	12	3
MDS-MLD	251	55
MDS-RS-MLD	3	0·7
MDS-EB-1	70	15
MDS-EB-2	92	20
MDS with isolated 5q-	6	1·3
MDS-U	8	2
Hb, g/l, median (range)	77 (31–153)	
ANC, × 10^9/l, median (range)	1·1 8 (0·04–11·19)	
PLT, × 10^9/l, median (range)	63 (2–1561)	
IPSS-R karyotype (Greenberg *et al*, 2012)		
Very good	5	1
Good	270	59
Median	113	25
Poor	26	6
Very poor	43	9
IPSS-R risk group (Greenberg *et al*, 2012)		
Very low	12	3
Low	115	25
Intermedia	152	33
High	92	20
Very high	86	19
Nazha model (Nazha *et al*, 2016)		
Low	131	29
Intermediate-1	165	36
Intermediate-2	117	26
High	44	10
Makishima model (Makishima *et al*, 2017)		
Low	27	6
Intermediate-1	263	58
Intermediate-2	121	27
High	46	10

ANC, absolute neutrophil count; Hb, haemoglobin; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; MDS-EB-1/2, MDS with excess blasts type 1/2; MDS-MLD, MDS with multilineage dysplasia; MDS-RS-MLD, MDS with ring sideroblasts (MDS-RS) with multilineage dysplasia; MDS-RS-SLD, MDS-RS with single lineage dysplasia; MDS-SLD, MDS with single lineage dysplasia; MDS-U, MDS unclassifiable; PLT, platelet count; WHO, World Health Organization.