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The Prognostic Significance of Chromosomal Abnormalities in Iraqi Myeloma Patients

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ABSTRACT

Background: Multiple myeloma, a cancer derived from plasma cells, accounts for 0.9% of global cancer cases, predominantly in developed countries. It leads to severe health complications including skeletal damage, renal failure, anemia, and increased infection risk. High-risk cytogenetic abnormalities like t(4;14), t(14;16), del(17p), and non-hyperdiploid karyotypes correlate with poor prognosis, necessitating cytogenetic evaluations in all newly diagnosed cases to direct treatment.

Aim: To assess the incidence, frequency, and impact of certain genomic abnormalities in a clinical course of newly diagnosed myeloma patient.

Methods: A cohort study, both retrospective and prospective, was performed on 60 diagnosed patients at Baghdad Medical City from October 2020 to June 2022. Data collected included demographics, comorbidities, bone marrow analysis, immunophenotyping by flow cytometry, cytogenetic studies via FISH, and blood tests. Treatment responses and survival rates were evaluated.

Results: The average age was 59.93 ± 11.15 years, with standard risk cytogenetics most prevalent. The VRD protocol was used in 60% of cases. The complete response rate was 36.7%, with an overall response rate of 68.3%. Patients with high-risk cytogenetics showed lower progression-free survival compared to those with normal or standard risk (p=0.017), although overall survival did not significantly differ among the groups (p=0.64).

Conclusion: Our research demonstrates that while the incidence of high-risk cytogenetics is slightly lower than global averages, such genetic risk factors significantly shorten progression-free survival. However, no notable difference was observed in overall survival among different cytogenetic risk groups.

KEYWORDS: Multiple myeloma, cytogenetic abnormalities, progression-free survival Short title: Impact of Cytogenetic Profiles on Multiple Myeloma Prognosis in an Iraqi Cohort.

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INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the uncontrolled proliferation of monoclonal plasma cells within the bone marrow. This disease results in significant morbidity due to extensive skeletal destruction, renal impairment, anemia, and immunodeficiency, largely attributed to the overproduction of monoclonal proteins.[i] Global estimates from the International Agency for Research on Cancer in 2018 reported MM as representing 0.9% of all new cancer diagnoses worldwide, with a rising incidence particularly noted in developed countries where diagnostic capabilities and population aging are prominent.[ii] The estimated age-standardized incidence rates of multiple myeloma for both sexes and all ages in Iraq in 2020 was 2.0 per 100,000. In the same year, 440 new cases were diagnosed (266 males and 174 females). Mortality related to multiple myeloma in Iraq during 2020 included 367 deaths (219 males and 148 females), with an age-standardized mortality rate of 1.7 per 100,000.[iii]

In-depth genomic studies have identified several cytogenetic abnormalities associated with MM, such as deletions, translocations, and chromosomal gains or losses. Notably, high-risk cytogenetics like t(4;14), t(14;16), and del(17p) have been linked to poorer prognoses. These genetic markers not only aid in disease classification but also significantly influence treatment decisions and prognosis, underscoring the importance of cytogenetic evaluation in newly diagnosed patients.[iv]

Hence in this study, we aimed to assess the incidence, frequency, and impact of certain genomic abnormalities in a clinical course of newly diagnosed myeloma patient.

SUBJECTS AND METHODS

This is a cross sectional study conducted between October 2020 and June 2022 at hematology department, Baghdad Medical City, Baghdad, Iraq. The inclusion a criterion was Patients diagnosed with multiple myeloma that had undergone cytogenetic assessment via FISH. And exclusion criteria were Patients younger than 18 years, those lost to follow-up, and those without

cytogenetic assessment. Various interventions and investigations were employed, including cytogenetic studies using FISH on bone marrow samples, immunophenotyping by flow cytometry, and standard blood tests such as complete blood count, serum protein electrophoresis, serum creatinine, and LDH levels.

The cytogenetic analysis in this study was conducted using the interphase FISH (iFISH) technique on bone marrow aspirate samples containing clonal plasma cells. These samples were processed using standard methods for uncultured samples and analyzed with specific probes for various translocations and deletions, including t(4;14), t(11;14), t(14;20), t(6;14), t(14;16), and del(17p), as well as for hyperdiploidy and trisomy. Each probe set was used to examine a total of 500 nuclei, utilizing Isis and Ikaros metasystem fluorescent microscopes. The International Myeloma Working Group (IMWG) criteria were used to classify symptomatic myeloma. Based on the cytogenetics results, patients were categorized into three risk groups: high-risk cytogenetics (HRC) included the presence of t(4;14), t(14;16), t(14;20), or del(17); standard risk cytogenetics (SRC) included hyperdiploidy, t(6;14), t(11;14), or trisomy; those without these specified abnormalities were classified into the negative iFISH group.[v]Out of the 60 patients in the study, 36 received a median of 6 cycles (ranging from 4 to 8 cycles, each lasting 28 days) of the VRD regimen, which includes bortezomib, lenalidomide, and dexamethasone. Another 23 patients were treated with the VCD regimen, comprising bortezomib, cyclophosphamide, and dexamethasone. One patient received the DVD regimen, which consists of daratumumab, bortezomib, and dexamethasone. The treatment regimens were based on specific comorbidities and drug availability.

Response assessment was performed using serum protein electrophoresis to measure the decrease in M component, which indicates remission in cases of secretory myeloma. For non-secretory myeloma, response was evaluated through bone marrow studies. Based on the International Myeloma Working Group (IMWG) criteria, responses were classified as complete response (CR), partial response (PR), very good partial response (VGPR), stable disease (SD), or progressive disease (PD).[5]

Ethical approval for the study was secured from the Scientific Committee at Baghdad National Center of Hematology and the Council of Iraqi Board for Medical Specialization.

For data analysis, the study employed IBM SPSS software, using Chi-square or Fisher's exact test for categorical data, and Student's t-test or Mann-Whitney U test for continuous variables. A p-value of less than 0.05 was considered statistically significant. Survival analysis was conducted using the Kaplan-Meier method with a log-rank test for comparing survival rates.

RESULTS

The study enrolled 60 participants aged between 33 and 80 years with a mean age 59.93 ±11.15 years. Standard risk cytogenetics were most commonly observed among the genetic tests conducted. The average percentage of bone marrow plasma cells was 49.33%, ranging from 10% to 97%. In terms of treatment response, 36.7% of patients achieved a complete response, 16.7% reached a very good partial response, 15% had a partial response, and 31.7% experienced progressive disease, resulting in an overall response rate of 68.3% (Table 1).

Table 1: Characteristics of myeloma patients and type of response

Variables		**No.**	**%**
Gender	Male	29	48.3
	Female	31	51.7
Genetic	SRC	31	51.7
	HRC	8	13.3
	Negative iFISH	21	35
Protocol	VRD	36	60
	VCD	23	38.3
	DVD	1	1.7
Type of immunoglobulin	IgG-K	31	51.7
	IgG-L	17	28.3
	IgA-K	7	11.7
	IgA-L	1	1.7
	Non-secretory	4	6.7
Type of response	CR	22	36.7
	VGPR	10	16.7
	PR	9	15
	PD	19	31.7

*SRC: standard risk cytogenetics; HRC: high risk cytogenetics; VCD: Bortezomib, cyclophosphamide and dexamethasone; VRD: Lenalidomide, Bortezomib, and Dexamethasone; DVD: Daratumumab in combination with bortezomib, dexamethasone; VGPR: Very good partial response; CR: complete response; PD: progressive disease; PR: partial response.

The lab investigations for patients are given in table 2.

Table 2: lab investigations

Investigations	**Mean ±SD**	**Range**

LDH (IU)	241.62 ±144.18	100-883
Albumin (mg/dl)	32.05 ±4.93	14-39
Serum creatinine (mg/dl)	1.7 ±1.4	0.2-6.7
Hemoglobin (g/l)	9.12 ±1.62	6.4-14

Cytogenetic testing revealed that the predominant cytogenetic alteration was t (11,14) in 28.3% of the cases, flowed by Hyperdiploidy in 20% of the cases, as shown in table 3.

Table 3: Frequency of cytogenetic alteration

Cytogenetics	**No.**	**%**
Negative iFISH	21	35
t (11,14)	17	28.3
Hyperdiploidy	12	20
t (4,14)	4	6.7
t (14,16)	2	3.3
t (6,14)	1	1.7
Del 17	1	1.7
Trisomy	1	1.7
t (14,20)	1	1.7

The response was higher with standard and negative iFISH than high risk groups, the type of response was not different statistically according to cytogenetic risk groups as shown in table 4.

Table 4: Association of different Cytogenetic risk group with response

Type of response	SRC	HRC	Negative iFISH	P value
	No. (%)	No. (%)	No. (%)	
CR	13 (41.9)	1 (12.5)	8 (38.1)	0.451
VGPR	5 (16.1)	1 (12.5)	4 (19)	
PR	6 (19.4)	1 (12.5)	2 (9.5)	
PD	7 (22.6)	5 (62.5)	7 (33.3)	

In the survival analysis of the study, the high-risk cytogenetic group (HRC) demonstrated the shortest mean progression-free survival at 8.25 ± 1.889 months, which was statistically significantly (p=0.017) lower compared to the standard risk cytogenetic group with a mean of 16.182 ± 1.463 months and the negative iFISH group at 11.4 ± 1.303 months (Figure 1).

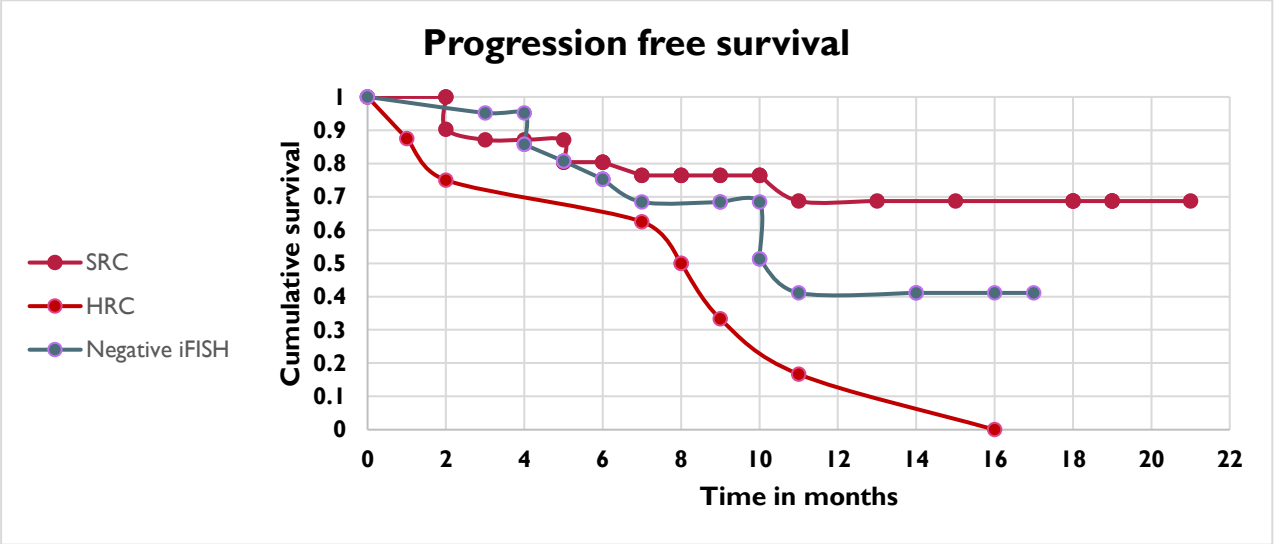

Figure 1: Progression free survival among different cytogenetic risk

Despite the significant differences in progression-free survival, the mean overall survival did not significantly differ among the groups (p=0.64). The HRC's mean overall survival was 11.8 ± 1.9 months, similar to the SRC and negative iFISH groups, which recorded 17.3 ± 1.3 months and 14.6 ± 1.3 months, respectively (Figure 2).

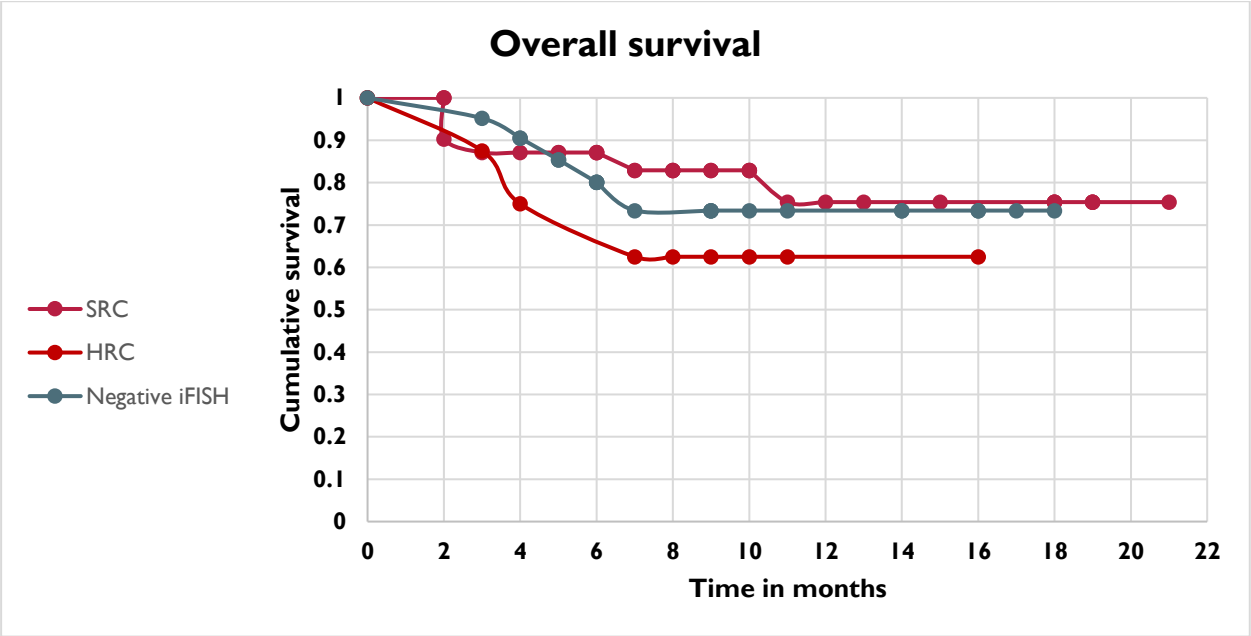

Figure 2: Overall survival of myeloma patients with different cytogenetic risk

DISCUSSION

The findings of our study bring forth insightful revelations on the prognostic significance of cytogenetic abnormalities in multiple myeloma, specifically within an Iraqi patient cohort.

In our study, high-risk cytogenetic abnormalities were identified in 13.3% of the participants, which is slightly lower than the generally estimated incidence of 15-20% reported by Kumar et al.[vi] This discrepancy might be attributed to several factors, including variations in the genetic background of the population studied, differences in diagnostic techniques, or the smaller sample size of our study which may not capture the full spectrum of cytogenetic diversity observed in larger cohorts.

In our study, we observed that LDH levels were elevated above normal across a range of values, reflecting findings similar to those reported by Rajkumar et al.[vii], who noted that higher LDH levels are linked to increased tumor burden, more aggressive disease, and poorer outcomes. Similarly, Sonneveld et al. found significant associations between high LDH levels and high-risk cytogenetic profiles.[viii]

In our study, the translocation t(11;14)(q13;q32) emerged as the most frequently observed cytogenetic abnormality, a finding that aligns with previous research,[ix, x] that indicate that this translocation, involving the cyclin D1 (CCND1) gene on chromosome 11 and the immunoglobulin heavy chain (IgH) locus on chromosome 14, is detected in approximately 15-20% of multiple myeloma cases. This translocation leads to the overexpression of CCND1, which plays a critical role in cell cycle regulation by promoting the transition from G1 to S phase, thus contributing to the proliferative advantage of myeloma cells. The consistent identification of this abnormality across studies confirms its role as a key driver of disease progression and suggests that targeting pathways associated with CCND1 may offer therapeutic benefits. Understanding the molecular implications of such translocations can help in refining treatment strategies and potentially improving outcomes for patients with specific cytogenetic profiles.[xi]

In our study, the type of therapeutic response did not differ significantly across different cytogenetic risk groups, contrasting with findings by Abdallah et al.[xii], who reported that high-risk cytogenetics (HRC) were associated with a poorer response to therapy in a larger cohort of 2027 patients.

Furthermore, the specific treatments administered can also influence outcomes across cytogenetic profiles. High-risk cytogenetics are often associated with resistance to standard therapies, but aggressive or novel treatment approaches might mitigate this effect, as suggested by studies exploring the efficacy of newer agents or combination therapies.[xiii, xiv]

Moreover, the stage of the disease at diagnosis and the precise mix of cytogenetic abnormalities present can also alter treatment outcomes. Research indicates that certain high-risk abnormalities may respond differently depending on the therapeutic regimen and the disease stage.[xv, xvi]

This discrepancy may be attributed to several factors. Firstly, the sample size and demographic characteristics of our study may differ substantially from those of Abdallah et al.[12], potentially influencing the statistical power and generalizability of the results. Additionally, variations in treatment protocols, the stage of disease at diagnosis, and other clinical interventions might also account for the differing impact of cytogenetic risk on treatment outcomes observed between the studies.[xvii]

After a median follow-up of ten months, our study observed that high-risk cytogenetics significantly correlated with a shorter

median progression-free survival compared to normal and standard risk cytogenetics. This was noted despite there being no significant difference in overall survival. This pattern aligns with findings by Abdallah et al.[11], who reported that patients with high-risk cytogenetic abnormalities typically experienced shorter PFS than those with standard-risk cytogenetics—14 months versus 30 months, respectively.

Furthermore, Chng et al.[xviii] highlighted that adverse cytogenetic abnormalities such as t(4;14), t(14;16), and del(17p) were linked to shorter PFS across both ixazomib-based and placebo-based treatment arms. Notably, the ixazomib-based treatment provided a relative improvement in PFS for patients with adverse cytogenetics, with a median PFS of 11.1 months compared to 6.8 months for those on placebo-based therapy.

CONCLUSION

Our research demonstrates that while the incidence of high-risk cytogenetics is slightly lower than global averages, such genetic risk factors significantly shorten progression-free survival. However, no notable difference was observed in overall survival among different cytogenetic risk groups. This divergence in progression-free and overall survival outcomes emphasizes the need for personalized treatment approaches that consider individual cytogenetic profiles, potentially enhancing therapeutic efficacy.

REFERENCES

1. [i]Jesus San-Miguel, Blade J. Multiple myeloma. In: A Victor Hoffbrand, Douglas R Higgs, David M Keeling, Mehta AB, editors. Postgraduate Haematology. 7th ed. Oxford, UK: John Wiley & Sons; 2016. p. 537-41.
2. [ii] Padala SA, Barsouk A, Barsouk A, Rawla P, Vakiti A, Kolhe R, et al. Epidemiology, Staging, and Management of Multiple Myeloma. Medical Sciences. 2021;9(1):3.
3. [iii] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today Lyon, France: : International Agency for Research on Cancer; 2020 [Available from: https://gco.iarc.fr/today.
4. [iv] Hanamura I. Multiple myeloma with high-risk cytogenetics and its treatment approach. Int J Hematol. 2022;115(6):762-777. doi:10.1007/s12185-022-03353-5
5. [v] Brigle K, Rogers B, editors. Pathobiology and diagnosis of multiple myeloma. Seminars in Oncology Nursing; 2017: Elsevier.
6. [vi] Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos MV, et al. Multiple myeloma. Nat Rev Dis Primers. 2017;3:17046.
7. [vii] Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(7):719-34.
8. [viii] Sonneveld P, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial. *J Clin Oncol*. 2023;41(8):1600-9.
9. [ix] Chesi M, Bergsagel PL. Molecular pathogenesis of multiple myeloma: basic and clinical updates. Int J Hematol. 2013;97(3):313-23.
10. [x] Avet-Loiseau H, Durie BG, Cavo M, Attal M, Gutierrez N, Haessler J, et al. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: an International Myeloma Working Group collaborative project. Leukemia. 2013;27(3):711-7.
11. [xi] Avet-Loiseau H, Durie BGM, Cavo M, et al. Combining fluorescent in situ hybridization data with ISS staging improves risk assessment in myeloma: the IFM experience. Blood. 2013;121(11):2059-2063.
12. [xii] Abdallah N, Rajkumar SV, Greipp P, Kapoor P, Gertz MA, Dispenzieri A, et al. Cytogenetic abnormalities in multiple myeloma: association with disease characteristics and treatment response. Blood Cancer J. 2020;10(8):82.
13. [xiii] Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus approach. Blood. 2016;127(24):2955-2962.
14. [xiv] Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.
15. [xv] Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. N Engl J Med. 2014;371(10):932-944.
16. [xvi] Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28(2):269-277.
17. [xvii] Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus approach. Blood. 2016;127(24):2955-2962.
18. [xviii] Chng WJ, Lonial S, Morgan GJ, Iida S, Moreau P, Kumar SK, Twumasi-Ankrah P, Villarreal M, Dash AB, Vorog A, Zhang X. A pooled analysis of outcomes according to cytogenetic abnormalities in patients receiving ixazomib-vs placebo-based therapy for multiple myeloma. Blood cancer journal. 2023 Jan 12;13(1):14.