Is IgA Isotype an Independent Adverse Prognostic Factor in Multiple Myeloma? A Systematic Review and Meta-Analysis of Cytogenetic Risk, Survival, and Treatment Outcomes in the Modern Era

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SOHO 2026

Keywords: multiple myeloma • immunoglobulin isotype • IgA myeloma • cytogenetics • meta-analysis

1 Context

The prognostic significance of the IgA isotype in multiple myeloma (MM) remains uncertain, particularly in the modern therapeutic era, where cytogenetic and molecular risk factors dominate risk stratification. Clarifying its independent impact is essential for accurate prognostication and clinical trial design. As novel agents reshape survival outcomes across myeloma subtypes, distinguishing isotype-specific risk from underlying cytogenetic risk has become increasingly important for clinicians and trialists alike.

2 Objective

To determine whether IgA isotype independently predicts overall survival (OS), progression-free survival (PFS), or treatment response after adjustment for cytogenetic risk and therapeutic era, and to clarify whether historically observed differences reflect isotype biology or confounding by high-risk genetic features.

3 Design

A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed, Embase, Web of Science, and Cochrane Library databases were searched from 2010 through March 2026. Random-effects models pooled hazard ratios (HRs) for OS and PFS comparing IgA and IgG isotypes, with heterogeneity quantified via the I^2 statistic. Subgroup analyses evaluated outcomes by cytogenetic risk and treatment regimen to isolate the independent contribution of isotype.

4 Setting

Multicenter retrospective cohorts, prospective trials, and registry analyses assessing modern multiple myeloma therapies across North America, Europe, and Asia, capturing a broad spectrum of real-world and trial-based treatment practices.

5 Participants

Thirty-five studies including more than 15,000 patients with newly diagnosed or relapsed multiple myeloma were analysed. Median follow-up exceeded 40 months in most datasets, allowing assessment of both early and long-term survival differences between isotypes.

6 Interventions

Triplet and quadruplet regimens incorporating proteasome inhibitors, IMiDs, monoclonal antibodies, and/or autologous transplantation — reflecting contemporary standard-of-care management across the included studies.

7 Main Outcome Measures

Hazard ratios for OS and PFS by immunoglobulin isotype, adjusted for cytogenetic risk factors including t(4;14), del(17p), and 1q gain.

Results

IgA vs IgG Classification → Cytogenetic Risk Assessment (FISH) → Adjusted Survival Modeling → **OS / PFS Comparison**

HR 1.05

adjusted OS, IgA vs IgG — no significant difference (95% CI 0.93–1.18)

HR 1.12

unadjusted PFS in IgA disease, attenuated after cytogenetic adjustment (95% CI 1.00–1.26)

15,000+

patients analysed across 35 pooled studies

- Across 35 studies including more than 15,000 patients, pooled analysis showed no significant difference in OS between IgA and IgG isotypes after adjustment for high-risk FISH abnormalities.
- Unadjusted analyses suggested modestly inferior PFS in IgA disease, but this difference was attenuated after controlling for cytogenetic risk, including t(4;14) and del(17p).
- IgA myeloma was associated with a higher prevalence of adverse cytogenetic features, including 1q gain and del(17p) ($p < 0.05$).
- Heterogeneity across studies was low, and no significant publication bias was detected.
- These findings suggest isotype-associated risk is largely explained by enrichment of high-risk cytogenetic abnormalities within the IgA subgroup.
- Together, these results argue for cytogenetic-based rather than isotype-based risk stratification in future trial design.

Conclusions

In the modern therapeutic era, IgA isotype does not independently confer inferior survival after accounting for cytogenetic risk. The historically perceived adverse prognosis likely reflects enrichment of high-risk cytogenetic abnormalities within the IgA subgroup rather than an intrinsic effect of isotype.

These findings support integrated risk stratification incorporating molecular and cytogenetic features rather than immunoglobulin isotype alone — informing more precise prognostic counseling and trial stratification.

Funding: None. **Conflict of Interest:** The authors declare no conflicts of interest.