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Impact of t(11;14) primary cytogenetic abnormality and the cumulative effect of multiple high-risk cytogenetics at diagnosis on the outcomes of patients with primary plasma cell leukemia

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To the Editor:

Primary plasma cell leukemia (pPCL) is a rare and aggressive variant of multiple myeloma (MM), marked by elevated clonal plasma cells (PCs) in the peripheral blood, accounting for ~1–2% of new MM cases [1]. Historically, it was defined as ≥20% circulating plasma cells (cPCs) and/or an absolute PC count $>2 \times 10^9$/L, but the International Myeloma Working Group (IMWG) revised this in 2013 to require only one of these criteria [2]. In 2021, following evidence that ≥5% cPCs conferred similarly poor outcomes as ≥20%, the IMWG further lowered the diagnostic threshold to ≥5% cPCs detected by peripheral smear [3]. At diagnosis, cytogenetic evaluation by fluorescence in situ hybridization (FISH) is essential for MM risk stratification. High-risk cytogenetic abnormalities (HRCAs), including t(4;14), t(14;16), t(14;20), del(17p)/monosomy 17, and gain/amplification of 1q21, portend poor prognosis [4]. While individual HRCAs adversely impact MM outcomes, the cumulative effect of multiple HRCAs further worsens clinical outcomes [5]; however, this cumulative impact remains less well defined in pPCL. Therefore, this study investigated the prognostic significance of cumulative HRCAs detected by FISH in pPCL patients receiving novel-agent-based induction. We retrospectively analyzed 100 consecutive patients diagnosed with pPCL at the Mayo Clinic Comprehensive Cancer Center between January 1, 2014, and December 31, 2024. Eligible patients met diagnostic criteria for MM with ≥5% cPCs on peripheral smear. FISH studies were performed on diagnostic bone marrow aspirates, and all patients received induction regimens incorporating novel agents. The study was approved by the Mayo Clinic Institutional Review Board in accordance with the Declaration of Helsinki. HRCAs were defined by the presence of any of the following t(4;14), t(14;16), t(14;20), del(17p)/monosomy 17 or gain/amplification of 1q. The primary endpoints were time to next therapy (TTNT) and overall survival (OS). TTNT was measured from the date of diagnosis to the initiation of subsequent therapy due to documented relapse or disease progression; patients who were alive or dead but relapse-free were censored at the last follow-up. OS was defined from the date of diagnosis to death from any cause, with surviving patients censored at the date of last contact. Kaplan–Meier estimates and log-rank tests were used for survival analysis, with Chi-square/Fisher exact and Wilcoxon rank-sum tests for categorical and continuous variables, respectively. Statistical significance was set at $P < 0.05$ (JMP v16.0.1, SAS Institute).

A total of 100 patients with newly diagnosed pPCL were included. Median follow-up was 48 months (95% CI: 40–60). Baseline characteristics are summarized in (Table S1). Median age was 64 years (range: 33–88); 45% were male. Median bone marrow plasma cell (BMPC) infiltration was 80% (range: 10–100), with 95% having ≥50% clonal BMPCs. Median cPCs percentage was 20% (range: 5–85), with 55% having ≥20% cPCs. Hypercalcemia (serum calcium ≥11 g/dL) was present in 33%, and 35% had serum creatinine ≥2 mg/dL. Intensive induction with continuous infusional chemotherapy was used in 17% of patients. Among the remaining 83 patients, 16 (19%) required salvage second-line therapy with a continuous infusional regimen due to early relapse following their initial induction. Quadruplet, triplet, and doublet-based therapies were used in 47%, 33%, and 20% patients, respectively. Autologous stem cell transplant (ASCT) was performed in 58%, including 53% who received it as part of upfront consolidation. IgH translocations were observed in 78% of patients; t(11;14) was the most common (39%). In this cohort, 75% of patients had ≥1 HRCAs: 40% had one, 28% had two, and 7% had three HRCAs (Fig. 1). t(11;14) was more frequent in patients without any HRCAs (88% vs. 23%, $P < 0.0001$) and was associated with more frequent hypercalcemia (47% vs. 24%, $P = 0.039$). Among HRCA-negative patients ($n = 25$), the median cPC was 24% (range: 5–75%) vs. 20% (range: 5–85%) in those with ≥1 HRCA ($P = 0.52$), suggesting that the overall burden of circulating disease at diagnosis was comparable across these two groups. We also compared the distribution of initial treatment approaches between patients with 0 versus ≥1 HRCA. Quadruplet-based regimens were used in 9/25 (36%) of patients without HRCAs and 38/75 (50.7%) of those with ≥1 HRCA ($P = 0.25$). Similarly, intensive chemotherapy was administered in 4/25 (16%) patients without HRCAs and 13/75 (17.3%) patients with ≥1 HRCA ($P = 1.00$). Thus, there were no significant differences in the initial treatment intensity between those with and without any HRCAs. Median TTNT and OS for the entire cohort were 18 months (95% CI: 12–20) and 47 months (95% CI: 37–100), respectively. Patients with 0 HRCAs had significantly longer TTNT and OS compared to those with ≥1 HRCA (22 vs. 13 months; 101 vs. 39 months; TTNT $P = 0.026$, OS $P = 0.006$) (Fig. 2A, B).

When assessing the impact of the cumulative HRCAs on TTNT and OS compared to those without any HRCAs, the median TTNT and OS for patients with 1 HRCA was 13 months (95% CI: 6–24) and 47 (95% CI: 37–106) respectively vs. 14 months (95% CI: 9–19) and 24 months (95% CI: 19–67) respectively for patients with >1 HRCAs (Fig. 2C, D). Among patients with t(11;14), those with no HRCAs ($N = 22$) had a median TTNT and OS of 21 months

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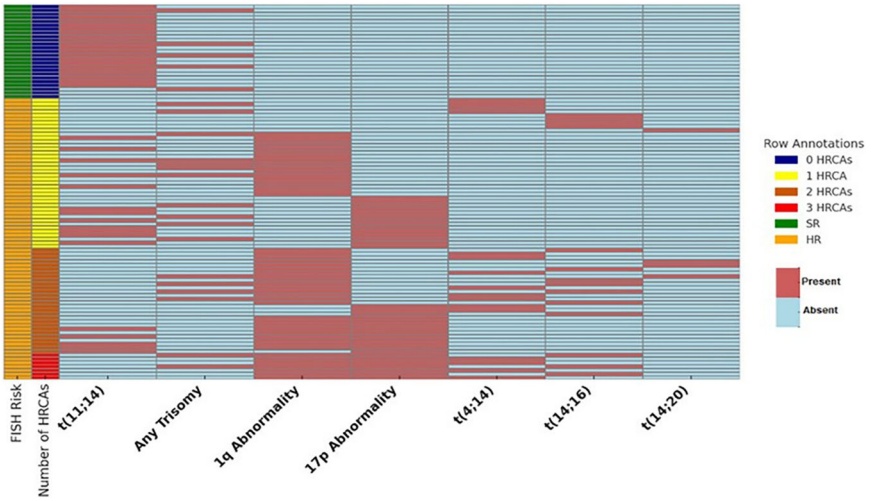

Fig. 1 Binary heatmap showing cytogenetic abnormalities in 100 patients with pPCL. Each row represents an individual patient; columns indicate the presence (red) or absence (light blue) of specific cytogenetic abnormalities detected by FISH at diagnosis. Left annotations denote FISH risk category and the number of HRCAs per patient. Abbreviations: pPCL primary plasma cell leukemia, FISH fluorescence in situ hybridization, HRCA high-risk cytogenetic abnormality.

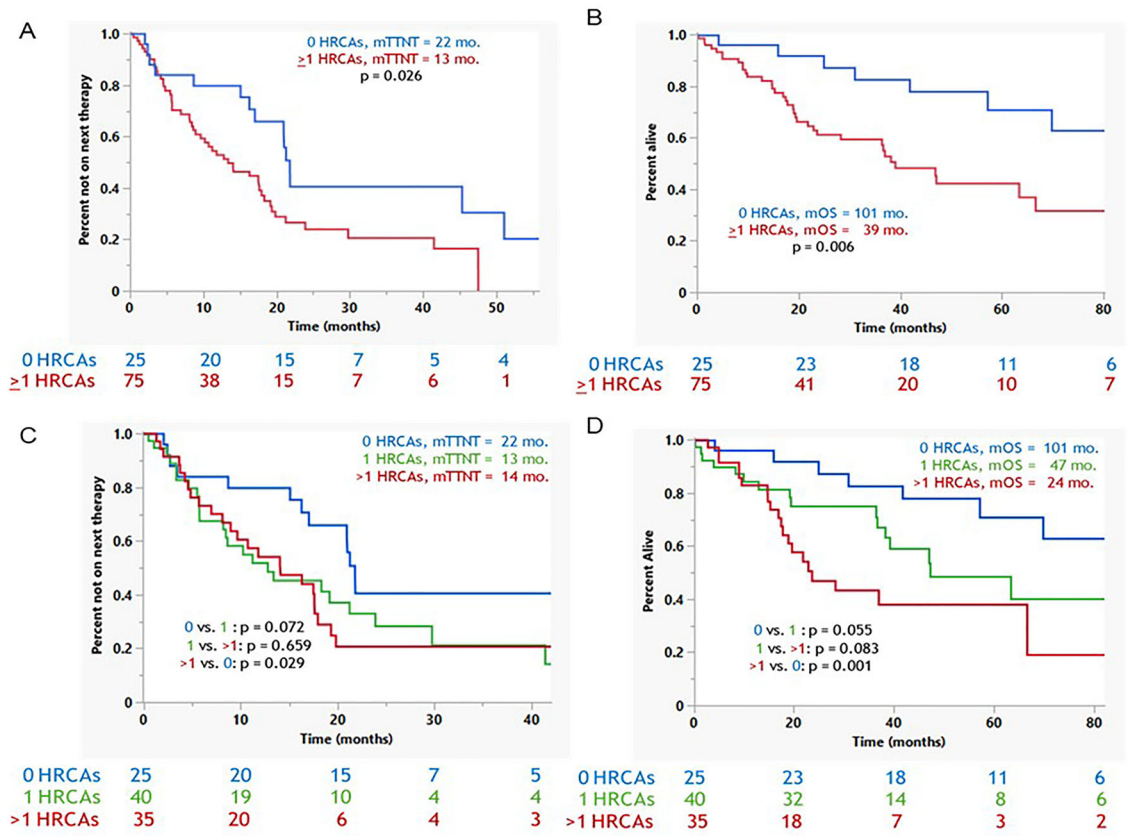

Fig. 2 Outcomes based on FISH cytogenetics. Kaplan-Meier curves of **A** TTNT and **B** OS stratified by the presence or absence of one or more HRCAs by FISH at diagnosis. Kaplan-Meier curves of **C** TTNT and **D**) OS stratified by the cumulative number of HRCAs (0 vs. 1 vs. >1) at diagnosis. Abbreviations: TTNT time to next treatment, OS overall survival, HRCA high-risk cytogenetic abnormality, FISH fluorescence in situ hybridization.

(95% CI: 15– 51) and 101 months (95% CI: 41–NR), respectively, compared to 18 months (95% CI: 7–41) and 47 months (95% CI: 5–NR) in those with one or more HRCAs (N = 17) (TTNT: P = 0.180, OS: P = 0.107)(Fig. S1A, B). To assess the impact of treatment-related factors on outcomes, we evaluated patients based on the number of therapeutic classes used in the induction regimen. Median TTNT and OS were 18 months (95% CI: 9–21) and 101 months (95% CI: 37–106) in those

receiving quadruplet-based induction, compared to 18 months (95% CI: 12–21) and 47 months (95% CI: 24–70) for those who didn't receive a quadruplet-based regimen (TTNT $P = 0.641$; OS $P = 0.083$))(Fig. S2A, B). Intensive induction was associated with median TTNT and OS of 18 months (95% CI: 10–45) and 111 months (95% CI: 23–111) versus 17 months (95% CI: 10–21) and 47 months (95% CI: 36–100) in non-intensive regimens (TTNT $P = 0.945$; OS $P = 0.251$) (Fig. S3A, B). Upfront ASCT ($N = 53$) resulted in longer TTNT and OS (21 months, 95% CI: 15–30; and 67 months, 95% CI: 42–NR) compared to those without ASCT ($N = 47$: TTNT 9 months, 95% CI: 6–18; OS 37 months, 95% CI: 22–106) (TTNT $P = 0.023$; OS $P = 0.032$)) (Fig. S4A, B). Of 96 evaluable patients, 51 (53%) achieved ≥CR as their best hematologic response. Those achieving ≥CR had significantly longer TTNT and OS (22 and 67 months) than those who did not achieve a ≥CR (6 and 36 months; TTNT $P < 0.0001$, OS $P = 0.011$) (Fig. S4C, D). Upfront ASCT, achieving ≥CR, and cumulative HRCA burden were evaluated in univariate and multivariate models (Table S2); only acheiving ≥CR and number of cumulative HRCAs consistently impacted the outcomes of TTNT and OS. In this retrospective cohort of pPCL, we observed that increasing HRCA burden at diagnosis was associated with a stepwise decline in TTNT and OS. While not all differences reached statistical significance, likely due to limited sample size, clear numerical trend supports the adverse cumulative impact of HRCAs. Thus, our findings suggest that both presence and accumulation of HRCAs contribute to more aggressive disease behavior in pPCL, echoing patterns seen in MM [5, 6]. Notably, nearly all HRCA-negative patients had t(11;14) as the primary cytogenetic event. Isolated t(11;14) was associated with prolonged OS (101 months) and TTNT (21 months), compared to 47 and 18 months in patients with t(11;14) plus additional HRCAs, supporting its favorable prognostic role when not accompanied by other HRCAs. This aligns with the French multicenter study [7], although their shorter OS may reflect higher HRCA co-occurrence or differences in access to novel therapies, such as Venetoclax or CAR-T cell therapy. In our cohort, 21% of t(11;14) patients received Venetoclax. BMPC burden didn't differ significantly between patients with isolated versus co-mutated t(11;14) ($p = 0.22$), suggesting distinct biology rather than disease bulk. Our findings reinforce the prognostic significance of HRCAs in pPCL and for the first time demonstrate the cumulative impact of multiple HRCAs as previously shown in MM. Furthermore, this study underscores the biological heterogeneity of pPCL, emphasizing the importance of recognizing distinct cytogenetic subgroups to guide personalized and effective treatment strategies. In particular, patients with isolated t(11;14) may derive substantial benefit from targeted therapies, such as BCL-2 inhibition [8–11]. These insights have important implications for future clinical trials and pPCL risk stratification. This study has several limitations, including its retrospective design and treatment heterogeneity that may introduce confounding results. A study by the Greek Myeloma Study Group demonstrated that triplet-based induction regimens, such as bortezomib, lenalidomide, and dexamethasone or daratumumab-based quadruplets induce deeper responses and improve OS compared to historical outcomes [12]. Furthermore, the frequent absence of FISH data for del(1p32), baseline β2M levels, LDH levels and the percentage of clonal PCs in S-phase of the cell cycle limited our ability to assess the applicability and prognostic performance of other factors in this population, such as the new IMS/IMWG high-risk definition [13–15]. Nonetheless, our study highlights the cytogenetic complexity and biological heterogeneity of pPCL, emphasizing the need for risk-adapted, personalized treatment strategies.

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DATA AVAILABILITY

Data is available upon reasonable request.

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AUTHOR CONTRIBUTIONS

T.H. and W.I.G. designed the research plan, analyzed the data and wrote the paper. S.K.K., S.S.A., A.A.D., A.D., D.J., F.K.B., D.D., S.Z., S.R.H., P.K., N.L., A.F., M.H., Y.L.H., E.M., R.W., T.V.K., J.C., M.B., N.A., Y.L., R.S.G., M.A.S., R.A.K., M.A.G., and S.V.R. critically reviewed and edited the final version of this letter.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL STATEMENT

This study was conducted with approval from the Mayo Clinic Institutional Review Board (IRB# 17-004935) and in accordance with the Declaration of Helsinki.

PATIENT CONSENT STATEMENT

Informed consent was obtained from all participants in the cohort.

ADDITIONAL INFORMATION

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