

Diagnosis to Transplant Interval as a Prognostic Factor in Newly Diagnosed Multiple Myeloma: a 30 Year Single Center Experience

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Abstract

Background

Autologous bone marrow transplant (ASCT) remains the cornerstone of multiple myeloma (MM) treatment. In developing countries, a lack of access to resources may lead to prolonged wait lists for ASCT, where patients are exposed to relapse and other morbidities. This project aims to evaluate the time from diagnosis to transplant interval, both as a continuous and categorical variable, and measure its effect on progression-free survival (PFS) of newly diagnosed transplant-eligible patients enrolled in our transplant center over a span of nearly 30 years.

Methods

We referred to a retrospective registry of ASCTs in Shariati Hospital, Tehran, Iran. Patients were included if they had a diagnosis of MM and underwent ASCT before their first relapse. The primary predictor was time of diagnosis to start of high-dose chemotherapy, and the primary outcome was PFS. PFS was expressed as both a continuous and categorical variable, and data were analyzed using the Cox proportional model of hazard ratios. To explore non-linear relationships, we utilized spline modeling, and to explore potential clinically relevant thresholds, we chose ROC-derived binary cutpoints, as well as a 12-month threshold from existing literature, and performed additional Cox proportional modeling.

Results

The median interval to transplant was 13.3 months (IQR 9.7–19.4). Early PFS was comparable across all groups, but patients with the longest delays experienced a pronounced decline in long-term outcomes. At five years, PFS was 35.6% for the longest-interval group compared to 46.1% for the intermediate group. Ten-year PFS dropped to 19.8% versus 30.3%. Cox models confirmed a higher risk of relapse or death with prolonged intervals (adjusted HR 1.37; 95% CI 1.09–1.72), while outcomes for the shortest-interval group were similar to the intermediate group. Each additional three-month delay was associated with a slight but noticeable increase in hazard (adjusted HR 1.02). ROC-based analyses suggested that intervals beyond roughly 17–19 months consistently predicted worse PFS.

Conclusions

Extended delays in transplantation (beyond 17 months) correlated with poorer progression-free survival, whereas shorter or moderate delays appeared less harmful. These results highlight the importance of timely access to ASCT while suggesting that small, unavoidable delays may be clinically acceptable.

Background

Despite major advances in its treatment in the last two decades, multiple myeloma (MM) remains incurable (1). Autologous stem cell transplantation (ASCT) remains the backbone of MM treatment (2). It involves the

collection of a patient's own hematopoietic stem cells, followed by a period of intense myelo-ablative chemotherapy, and the reintroduction of said stem cells to restore normal blood cell production (3).

Eligible patients usually receive 3–6 months of induction chemotherapy (4). Typically, stem cell collection is conducted 3–4 weeks after the last induction period (5). Subsequently, patients receive high-dose myeloablative chemotherapy (melphalan), and stem cells are reinfused (6, 7). Although upfront and early transplant for eligible patients is the most agreed-upon treatment in the literature, access to transplant is often delayed in developing or resource-limited settings (8). The transplant process (from high-dose chemotherapy to when blood markers rise back up) usually requires hospitalization along with isolation and can last up to 4 weeks (9, 10). As a result, bone marrow transplant wards usually face logistical issues with beds being occupied for prolonged periods. Ultimately, many patients are exposed to a lengthy period between the end of their induction therapy and transplant.

While it is intuitive that very prolonged delays should be associated with worse transplant outcomes, mainly progression-free survival, the exact effect of the diagnosis-to-transplant interval remains elusive (11, 12). Most papers categorize the diagnosis-to-transplant interval into early (< 12 months) and delayed (> 12 months), and although previous work has evaluated this topic, contradictory reports exist (13–15). Moreover, to our knowledge, no effort has been made to identify a safe "transplant window", where moderate delays in transplant are tolerable. The diagnosis to transplant interval and its potential impact are especially important for health systems, where knowing an estimated window for ASCT allows for better planning.

In this context, we decided to evaluate the time from diagnosis to transplant interval, both as a continuous and a categorical variable, and to assess its effect on progression-free survival (PFS) in newly diagnosed transplant-eligible patients enrolled at our transplant center over nearly 20 years.

Methods

In this retrospective cohort study, we referred to a pre-existing internal registry of transplant patients in Shariati Hospital, Iran. We included if they had a diagnosis of multiple myeloma and underwent their first autologous hematopoietic cell transplantation (ASCT) at Shariati Hospital, Tehran, Iran from 1996 to 2022. Patients who relapsed before transplant, expired, or had relapsed before hospital discharge were excluded. Individuals were required to have valid calendar dates for primary diagnosis, ASCT, and post-transplant follow-up. Relapse records without a valid relapse date or relapses occurring after the last documented follow-up were not considered valid events.

The derivation of the analytic cohort is shown in Fig. 1. After applying these criteria, 1,196 patients had a plausible interval from diagnosis to ASCT and were included in descriptive analyses. Of these, 1,186 patients had complete information on age and sex and formed the final cohort for survival modeling. Patient data were extracted from the hospital's ASCT registry, which contains information on demographics, laboratory results, disease characteristics, and follow-ups.

Induction Therapy

Almost all patients received Bortezomib-Thalidomide-Dexamethasone (VTd) or Bortezomib-Lenalidomide-Dexamethasone (VRd) (16, 17). Induction typically lasted 3 to 6 months, depending on patient response and clinical discretion. Stem cell collection was scheduled 3–4 weeks after the last induction cycle and granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood stem cells (CD34 + $\geq$ 2 million/kg) were collected.

Transplant protocol

Transplant protocol

Patients were evaluated for eligibility in a transplant clinic and were informed regarding the procedure, potential risks, and benefits. High-dose melphalan (200mg/m²) was used for myeloablation, and patients with renal impairments received a lower dose (140 mg/m²). Previously collected stem cells were reinfused after conditioning, and mobilization was given based on daily blood counts during hospitalization.

Exposure: interval from diagnosis to ASCT

The principal exposure was the interval between primary myeloma diagnosis and ASCT. The interval was calculated as the difference in days between the diagnosis and ASCT dates, then converted to months using a standard conversion factor. Negative or zero values, reflecting impossible or same-day sequences, were set to missing.

Interval was analyzed in two complementary ways. First, we categorized it into tertiles based on its empirical distribution, resulting in groups representing short, intermediate, and long intervals. The intermediate tertile was chosen as the reference category, as it corresponded to routine clinical practice and showed the most favorable survival pattern in exploratory analyses. Secondly, the interval was modeled as a continuous variable, expressed per 3-month increase, to provide an easily interpretable estimate of risk per unit of postponement.

Outcomes and follow-up

The primary endpoint was progression-free survival. PFS was defined as the time from the date of ASCT to relapse or death from any cause, whichever occurred first. We applied a strict hierarchy: when relapse and death were recorded on the same date, relapse was taken as the defining event. Deaths in patients without a prior relapse were also counted as PFS events. Patients who were alive and free from relapse at their last recorded contact were censored at that date.

Follow-up time was measured in months. Kaplan–Meier estimates were used to describe PFS over the entire observation period and at prespecified horizons of 2, 5, and 10 years after HCT, representing early, intermediate, and long-term disease control.

Baseline variables and covariates

Baseline variables were age (at the time of diagnosis), gender, the type of light-chain, mobilization therapy, Karnofsky performance score, blood group and Rh factor, and collected CD34 + cells. Laboratory variables were white blood cells (WBC), platelet count, liver enzymes, bilirubin, lactate dehydrogenase (LDH), and creatinine. Continuous variables are reported as medians with interquartile ranges, and categorical variables as counts and percentages.

Statistical analysis

Baseline characteristics were compared across interval tertiles using Kruskal–Wallis tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables. Kaplan–Meier curves were constructed to visualize PFS by interval tertile, and differences were assessed using the global log-rank test. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for interval tertiles and for interval modeled continuously, both unadjusted and adjusted for age and sex.

To evaluate potential non-linearity in the association between interval and PFS, natural cubic spline models were fitted and compared with linear specifications using likelihood-ratio tests. Spline results were presented graphically and truncated at 50-month intervals to avoid unstable estimates due to sparse data. Proportional hazards assumptions were assessed using Schoenfeld residuals.

To further examine whether clinically or empirically defined thresholds for the diagnosis-to-ASCT interval were associated with PFS, we performed additional binary cutpoint analyses. First, we evaluated a prespecified clinically relevant threshold of 12 months, classifying patients as having undergone HCT before 12 months versus at or after 12 months from primary diagnosis. This threshold was selected because 12 months is commonly used in the transplant literature to distinguish early from delayed autologous transplantation (13, 18, 19).

Second, we explored data-driven thresholds using time-dependent receiver operating characteristic (ROC) analysis at two prespecified post-ASCT horizons: 5 years and 10 years. These horizons were selected to represent intermediate and long-term disease control. For each horizon, the interval value that maximized the Youden index was identified as the optimal exploratory cutpoint (20). Patients were then categorized according to whether their diagnosis-to-ASCT interval was below or above the ROC-derived threshold.

For each binary cutpoint, Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for PFS. Models were fitted both unadjusted and adjusted for age at diagnosis and sex. Time-dependent ROC performance was summarized using the area under the curve (AUC) and the Youden index. Because the thresholds were selected from the same dataset, they were considered exploratory and interpreted as hypothesis-generating rather than definitive thresholds.

All analyses were conducted using R, and statistical significance was defined by a two-sided p-value < 0.05.

Ethical considerations

This project was approved by the institutional review board (IR.TUMS.HORCSCT.REC.1404.030) prior to commencing.

Results

Study Cohort

The flow of patients through the study is summarized in Fig. 1. After excluding individuals without usable information on ASCT timing or follow-up, 1,196 patients with multiple myeloma and ASCT had a non-missing, plausible interval from primary diagnosis to transplantation and contributed to the descriptive analyses. Among these, 1,186 also had complete data on age and sex and formed the cohort for Cox regression models of PFS.

Baseline characteristics by interval tertiles

Across the whole cohort, the median interval from diagnosis to ASCT was 13.3 months (IQR 9.7–19.4). By design, the three tertile groups represented short (T1, ≤ 11.0 months; $n = 399$), intermediate (T2, $> 11.0 - \leq 17.0$ months; $n = 400$) and long (T3, > 17.0 months; $n = 397$) intervals (Table 1). Age at diagnosis differed statistically across tertiles, although the absolute differences were modest: the median age was 53.6 years in T1, 54.3 years in T2, and 52.1 years in T3 ($p < 0.001$). Men comprised around two-thirds of the cohort, and the distribution of sex, Rh factor, and ABO blood group was similar across interval categories (all $p > 0.05$). Mobilization status, Karnofsky performance score, and graft cell doses were also well balanced. The only laboratory variable showing a statistically significant difference was baseline platelet count, which was slightly lower in the longest-interval tertile (median $167 \times 10^9/L$ in T3 vs $191.5 \times 10^9/L$ and $197.0 \times 10^9/L$ in T1 and T2, respectively; $p = 0.022$). Other liver and renal function markers were broadly comparable (Table 1).

Table 1
Baseline characteristics of multiple myeloma patients by tertiles of interval from primary diagnosis to autologous HCT.

Variable	Overall	T1	T2	T3	P value*
N	1196	399	400	397	
Interval to HCT, months (tertiles: ≤11.0, > 11.0–≤17.0, > 17.0)	13.3 (9.7–19.4)	8.6 (7.4–9.7)	13.3 (12.1–14.9)	23.2 (19.4–32.5)	< 0.001
Age at diagnosis, years	53.3 (46.8–58.5)	53.6 (47.2–58.9)	54.3 (47.7–59.6)	52.1 (45.7–57.2)	< 0.001
Male, n (%)	751 (62.8%)	256 (64.3%)	245 (61.2%)	250 (63.0%)	0.667
Rh positive, n (%)	935 (90.7%)	303 (89.9%)	314 (90.0%)	318 (92.2%)	0.508
Blood group O, n (%)	379 (36.8%)	122 (36.2%)	126 (36.1%)	131 (38.0%)	0.679
Mobilization given, n (%)	46 (9.9%)	19 (12.0%)	17 (11.0%)	10 (6.5%)	0.222
Karnofsky performance score	90.0 (90.0–90.0)	90.0 (90.0–90.0)	90.0 (90.0–90.0)	90.0 (90.0–90.0)	0.258
WBC at baseline, ×10 ⁹ /L	15.8 (6.9–25.6)	15.3 (6.8–24.1)	14.9 (6.4–26.1)	16.9 (7.1–25.6)	0.852
Platelets at baseline, ×10 ⁹ /L	185.0 (145.0–234.8)	191.5 (150.0–245.5)	197.0 (148.0–238.0)	167.0 (136.0–214.0)	0.022
SGOT at baseline, U/L	18.0 (14.0–23.0)	18.0 (14.0–22.0)	17.0 (14.0–22.0)	18.0 (14.8–24.0)	0.323
Bilirubin at baseline, mg/dL	0.7 (0.5–1.0)	0.7 (0.5–0.9)	0.7 (0.5–1.0)	0.7 (0.6–1.0)	0.283
LDH at baseline, U/L	356.5 (290.0–454.0)	354.0 (283.0–448.8)	359.0 (292.0–491.8)	354.0 (303.2–440.8)	0.682
Creatinine at baseline, mg/dL	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.2)	0.9 (0.8–1.1)	0.242
CD34 + cells in graft, ×10 ⁶ /kg	2.9 (1.8–4.5)	3.2 (1.8–4.8)	3.0 (1.9–4.4)	2.7 (1.6–4.3)	0.112

*P-values are from Kruskal–Wallis tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables, and assess overall differences across the three interval tertiles.

Relapse-free survival and time horizons

Figure 2 shows Kaplan–Meier curves for PFS by tertiles of the time interval from diagnosis to ASCT. Early survival is similar, but with longer follow-up, the curve for the longest-interval group drops below those for the shortest and intermediate groups. The p-value of 0.023 is from the global log-rank test, indicating that PFS differs significantly across interval tertiles over the entire follow-up period.

Cox models: tertiles and continuous interval

Cox models confirmed that a prolonged interval was associated with inferior PFS (Table 3). In unadjusted analyses with the intermediate tertile as the reference, the hazard ratio (HR) for the shortest interval group (T1) was 1.11 (95% CI 0.89–1.38; $p = 0.370$), indicating no evidence that very early transplantation improved outcomes compared with the mid-range interval. In contrast, patients in the longest-interval tertile (T3) experienced significantly higher risk of relapse or death, with an HR of 1.35 (95% CI 1.08–1.70; $p = 0.008$) versus T2.

Adjustment for age and sex had little impact on these estimates. The adjusted HR for T1 versus T2 was 1.12 (95% CI 0.89–1.40; $p = 0.331$), while the HR for T3 versus T2 was 1.37 (95% CI 1.09–1.72; $p = 0.006$). Thus, ASCT intervals beyond roughly 17 months after diagnosis were associated with a 37% higher hazard of relapse or death.

Treating the interval as a continuous variable yielded results close to those obtained with the discrete approach. Each additional 3-month increase in interval was associated with a 2% increase in the hazard of a PFS event (adjusted HR per 3 months 1.02, 95% CI 1.00–1.03), with a p -value of 0.058, just above the conventional threshold for statistical significance (Table 3).

Table 2
Cox regression models for relapse-free survival according to tertiles and continuous intervals from primary diagnosis to autologous HCT.

Model	Exposure	HR(CI)	P value	N	Events
Model 1: Tertiles (unadjusted)	T1 (shortest interval) vs T2 (intermediate interval)	1.11 (0.89–1.38)	0.370	1,186	491
Model 1: Tertiles (unadjusted)	T3 (longest interval) vs T2 (intermediate interval)	1.35 (1.08–1.70)	0.008	1,186	491
Model 2: Tertiles (adjusted for age, sex)	T1 (shortest interval) vs T2 (intermediate interval)	1.12 (0.89–1.40)	0.331	1,186	491
Model 2: Tertiles (adjusted for age, sex)	T3 (longest interval) vs T2 (intermediate interval)	1.37 (1.09–1.72)	0.006	1,186	491
Model 3: Continuous (unadjusted)	Interval, per 3-month increase	1.02 (1.00–1.03)	0.081	1,186	491
Model 4: Continuous (adjusted for age, sex)	Interval, per 3-month increase	1.02 (1.00–1.03)	0.058	1,186	491

Hazard ratios (HRs) and 95% confidence intervals (CIs) for relapse-free survival (PFS) after autologous ASCT in multiple myeloma, according to the interval from primary diagnosis to ASCT. Tertile models use the intermediate interval tertile (T2) as the reference group, providing comparisons for the shortest interval tertile (T1) and the longest interval tertile (T3). Continuous models estimate the relative hazard per 3-month increase in the interval. Adjusted models include age at diagnosis (years) and sex as covariates. Time zero is the date of ASCT, and PFS events are defined as relapse or death without prior relapse, with relapse taking precedence when both are recorded on the same date.

Spline analysis of the interval–PFS association

To explore potential non-linear effects of interval, we fitted a Cox model with natural cubic splines for interval, adjusted for age and sex (Fig. 3). The estimated hazard ratio curve showed a shallow trough around the lower tertile cut-point, followed by a gradual increase in hazard with longer intervals. However, the confidence bands were wide, particularly toward the extremes of the observed range. A likelihood-ratio test comparing the spline model with the simpler linear specification produced a p-value of 0.741, providing no evidence that a more complex, non-linear functional form improved model fit. Overall, the spline analysis supports the interpretation that the adverse effect of interval is modest and approximately linear within the range of intervals represented in this cohort, with the most consistent disadvantage observed for patients whose transplantation was substantially postponed beyond the upper tertile.

Binary interval cutpoints and ROC-derived thresholds

To examine the binary interval cutpoint, we used three cutpoints: (i) a clinically relevant threshold at 12 months was not related to PFS. (ii) ROC-based thresholds identified more adverse risk groups. When 5 years was considered as the time horizon, a time-dependent ROC analysis, a cutpoint of 18.6 months (AUC 0.547, Youden 0.111); patients with an interval of more than 18.6 months had an adjusted HR of 1.33 (95% CI 1.10–1.62; $p = 0.004$). (iii) Considering 10-year PFS as the horizon, time-dependent ROC analysis yielded 16.8 months as the optimal cutpoint with an adjusted HR of 1.27 (95% CI 1.05–1.53; $p = 0.013$). Overall, long intervals above an approximate cutpoint of 17–19 months consistently conferred modestly worse PFS, while discrimination remained limited (Table 4).

Table 3

Cox regression models for relapse-free survival using binary interval cutpoints, including a 12-month threshold and ROC-derived thresholds at 5 and 10 years.

Model	Exposure	Cutpoint months	Horizon	HR (95% CI)	P value	N	Events	AUC	Youden
Model 1: 12-month cutpoint (unadjusted)	Interval ≥ 12 vs < 12 months	12.0		1.05 (0.87–1.25)	0.628	1,186	491	NA	NA
Model 2: 12-month cutpoint (adjusted for age, sex)	Interval ≥ 12 vs < 12 months	12.0		1.05 (0.88–1.25)	0.616	1,186	491	NA	NA
Model 3: ROC 5-year cutpoint (unadjusted)	Interval ≥ 18.6 vs < 18.6 months (ROC at 5 years)	18.6	5 years	1.32 (1.09–1.60)	0.005	1,186	491	0.547	0.111
Model 4: ROC 5-year cutpoint (adjusted for age, sex)	Interval ≥ 18.6 vs < 18.6 months (ROC at 5 years)	18.6	5 years	1.33 (1.10–1.62)	0.004	1,186	491	0.547	0.111
Model 5: ROC 10-year cutpoint (unadjusted)	Interval ≥ 16.8 vs < 16.8 months (ROC at 10 years)	16.8	10 years	1.26 (1.05–1.51)	0.015	1,186	491	0.536	0.547
Model 6: ROC 10-year cutpoint (adjusted for age, sex)	Interval ≥ 16.8 vs < 16.8 months (ROC at 10 years)	16.8	10 years	1.27 (1.05–1.53)	0.013	1,186	491	0.536	0.547

Discussion

This study evaluated the impact of the time interval between diagnosis and ASCT on progression-free survival in newly diagnosed, transplant-eligible multiple myeloma. A longer interval was associated with poor PFS and was most apparent in patients in the third tertile, whereas patients in T2 (11 < interval < 17 months) and T1 (< 11 months) experienced roughly similar outcomes. When modeled continuously, the effect of delay appeared insignificant, but became more profound with longer delays and longer follow-ups. Our exploratory spline analysis suggested that the relationship between interval and PFS was approximately linear rather than nonlinear, while binary threshold analyses indicated that worse outcomes were more likely to emerge beyond an interval of around 16.8 to 18.6 months. These findings suggest that the issue may not be about whether

ASCT can be performed as early as possible, but whether it is conducted inside a certain tolerable window. Our data support a more nuanced interpretation in which some delay may be acceptable.

The most common method of categorizing patients by transplant interval in the literature has been to divide patients into two groups based on a 12-month cutoff, resulting in early (< 12 months) and late (> 12 months) intervals. In a retrospective analysis of 514 patients undergoing ASCT, Leng et al. found no difference in PFS between the early and late groups (40 vs. 37 months; $P = 0.552$) despite a deeper response rate before and after ASCT and greater use of lenalidomide-based maintenance therapy in the early group. The median time to ASCT for the early and late groups was reported as 7.7 and 22.3 months, respectively. Similarly, our 12-month cutpoint did not discriminate between PFS, whereas our tertile model showed that the longest interval group (T3) displayed significantly worse PFS compared with the intermediate group (T2) with HR 1.37, 95% CI 1.09–1.72, $p = 0.006$. Our ROC-derived analyses also pointed in the same direction and showed adverse cutpoints around 16.8 to 18.6 months.

In contrast, a 2022 paper by Kumar et al. found superior response rates and PFS (69.5 versus 50 months; $P < 0.05$) in a retrospective analysis of 363 patients (21). They also evaluated the impact of time of diagnosis to transplant on mobilization and stem cell harvest. Median number of harvest sessions was 2 in both groups, but the number of adequate CD34 + harvests was lower in the late group. In addition, a greater proportion of patients in the late group require plerixafor (16.7% versus 7%; $P < 0.02$).

Several mechanisms may explain why prolonged intervals were associated with poor PFS. A prolonged diagnosis-to-transplant interval provides the disease with the chance to relapse before ASCT happens. It may also enable complications such as chemotherapy-related morbidities or deterioration in patient fitness, even when our baseline covariates do not capture such differences. As reported by Leng et al., the delayed transplant group was associated with advanced age and lower melphalan doses (10% of patients received < 200 mg/m² in the early SCT group vs. 22% in the delayed group; $P = .001$)(22). Leng et al. did not come up with a reason as to why no difference in PFS could be found. We believe, at least in part, that this finding was due to the binary categorization of patients into early and late cohorts.

We used a combination of spline modeling and binary cutpoint approaches to explore the shape of the association between the diagnosis-to-transplant interval and PFS. The spline analysis failed to identify strong evidence of non-linearity and displayed very wide confidence intervals. The ROC-derived cutpoints of 16.8 and 18.6 months were associated with inferior PFS and were consistent with the hazard ratios observed in the longest tertile in our Cox analysis. However, their discriminatory performance was limited, as reflected by low AUC values.

These findings are particularly relevant for health systems in which access to transplantation is constrained. A lack of transplant centers, limited bed availability, financial barriers for both patients and hospitals, and logistical problems (having to travel in order to access transplants) all contribute to delays in transplantation. From a systems perspective, we support efforts to minimize avoidable delays, but highlight that some delays may be affordable by the system and the patient.

This study included a relatively large cohort of transplanted patients and allowed for examination of the diagnosis-to-transplant interval from multiple angles. Our findings across Kaplan-Meier graphs, Cox models,

and spline modeling indicate that the observed association is not a product of one analytic approach. Adjustment for age and sex had very little effect on HRs when comparing the longest and intermediate tertiles, which also strengthens our results. Several limitations should be acknowledged. First, the cohort includes data from about two decades ago, and in-depth data regarding disease status (molecular testing, biochemistries) for many patients were unavailable. As a result, our adjustment was limited, and we could not account for some critical variables that could confound our results. Second, the study focused on patients who ultimately underwent ASCT and did not address patients who relapsed before ASCT or were not eligible at all. Third, progression-free survival was the primary endpoint, and overall survival data for the majority of patients were lost to time. It should be noted, though, that overall survival in multiple myeloma transplant studies tends to be equal across comparison groups (23). Finally, our ROC-derived cutpoints should be interpreted cautiously as their performance was limited and they would be better viewed as exploratory rather than definitive.

Future studies should aim to distinguish and address biologic and health-system drivers of delays. External validation in other cohorts will also be important to determine whether the numbers identified here are reproducible. It would be critical to address variables such as response depth, fluorescence in situ hybridization (FISH) studies, and disease risk group in future work. It should also be noted that this project did not take into account patients who relapsed before ASCT and underwent salvage transplants. Recent literature has failed to establish a survival benefit with upfront ASCT compared to salvage ASCT, though a PFS benefit has been established (24, 25).

In short, our findings suggest that prolonged intervals (> 17 months) from diagnosis to ASCT are associated with poor PFS in newly diagnosed multiple myeloma. In contrast, transplantation within the shortest interval range does not seem to differ from ASCT over an intermediate timeframe.

Conclusion

In this retrospective study examining the time of diagnosis to transplant interval among 1186 patients with newly diagnosed MM, we concluded that a prolonged interval was associated with poor PFS in general. This adverse association was most evident in patients with the longest delays, whereas outcomes were similar between short and moderate interval groups. We suggest that the clinically relevant concern may be excessive postponement rather than failure to perform transplantation at the earliest possible time. Exploratory analyses suggested that the adverse signal became more apparent beyond approximately 17 to 19 months, though these thresholds should be interpreted cautiously. Overall, our findings support efforts to minimize avoidable delays to transplantation, particularly in settings where resources are limited.

Abbreviations

PFS

Progression free survival

OS

overall survival

ASCT

Autologous stem cell transplant

FISH

fluorescence in situ hybridization
ROC
Receiver operating characteristic
AUC
Area under the curve
KPS
Karnofsky performance score
WBC
White Blood Cell
Hb
Hemoglobin
LDH
Lactate dehydrogenase
SGOT
Serum Glutamic Oxaloacetic Transaminase
VTd
Velcade (bortezomib) + Thalidomide + dexamethasone
VRd
Velcade (bortezomib) + Revlimid (lenalidomide) + dexamethasone

Declarations

Ethics approval and consent to participate

This project was approved by the research ethics committee of school of medicine – Tehran University of Medical Sciences, Tehran, Iran (Approval No. IR.TUMS.HORCSCT.REC.1404.030) prior to commencing. The requirement for informed consent was waived due to the retrospective nature of the study and the use of de-identified data. All research was carried out in accordance to the Helsinki Declaration.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Author Contribution

ST, SR, MV, and GJ were senior staff at the research center and were involved in project design, as well as overseeing data acquisition. MMK and DY analyzed the data and provided a primary draft, while HK, MV, MB and FN finalized it. All authors provided meaningful revisions and approved the final version.

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Not applicable

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

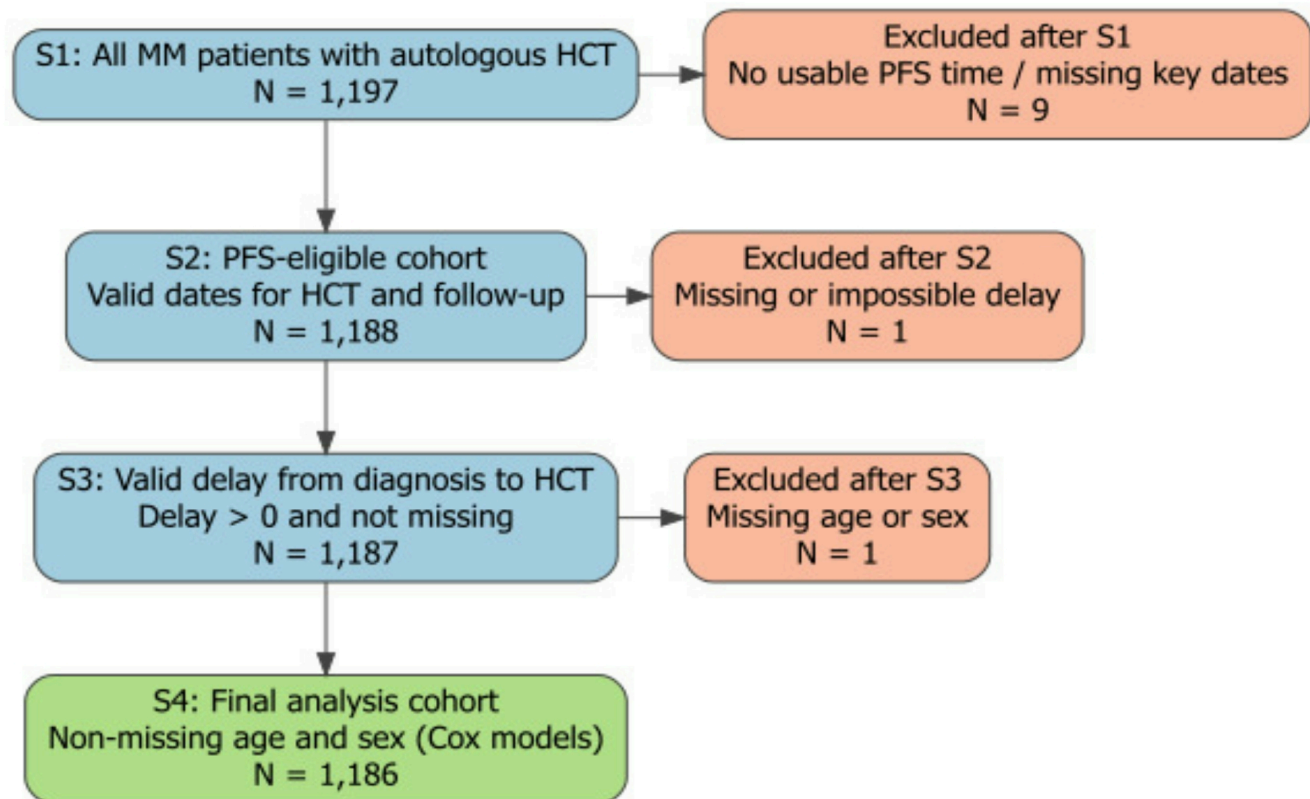


Figure 1

Flow diagram of the study cohort for relapse-free survival analyses.

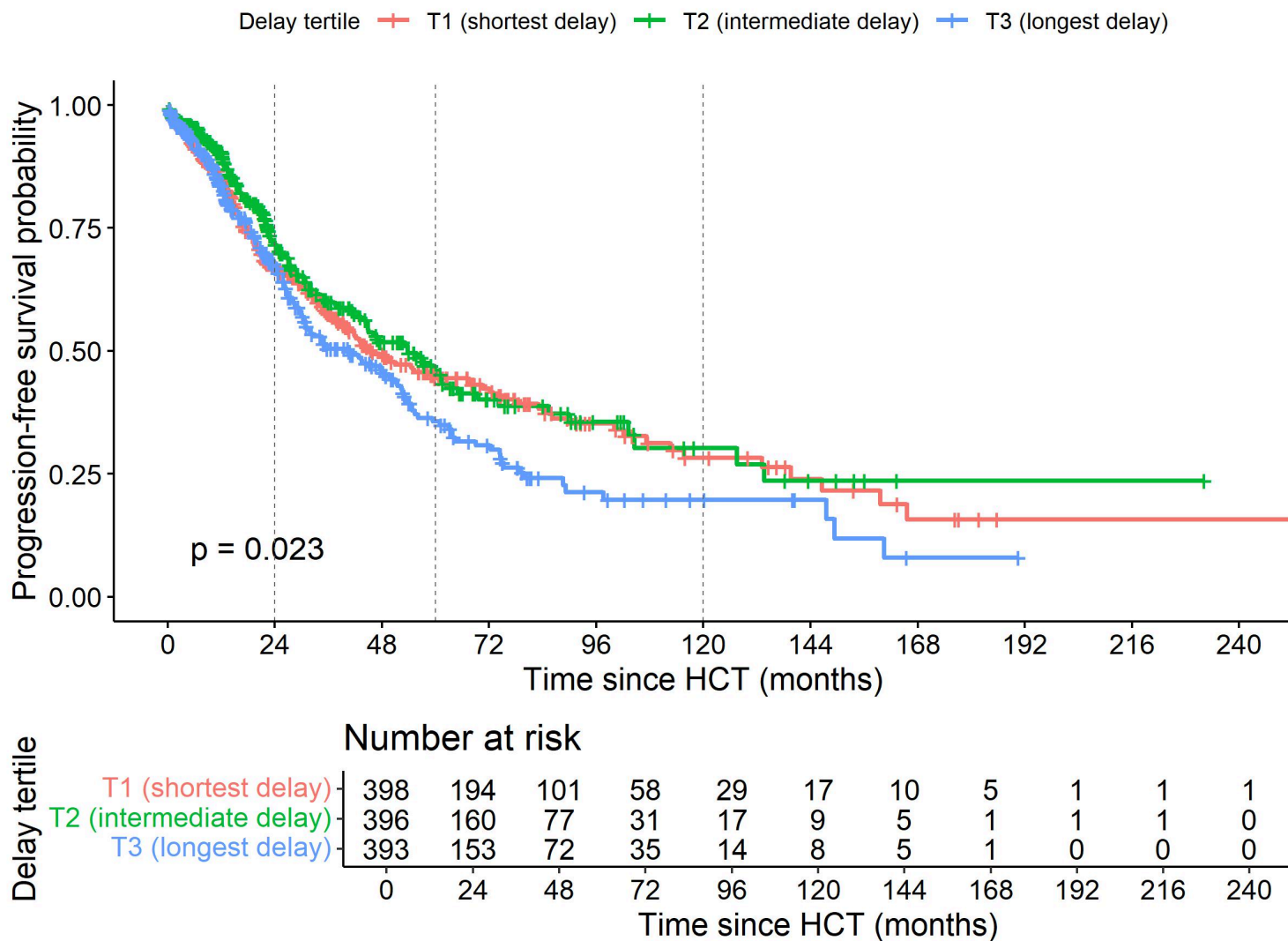


Figure 2

Kaplan–Meier curves for relapse-free survival by tertiles of interval from primary diagnosis to autologous ASCT.

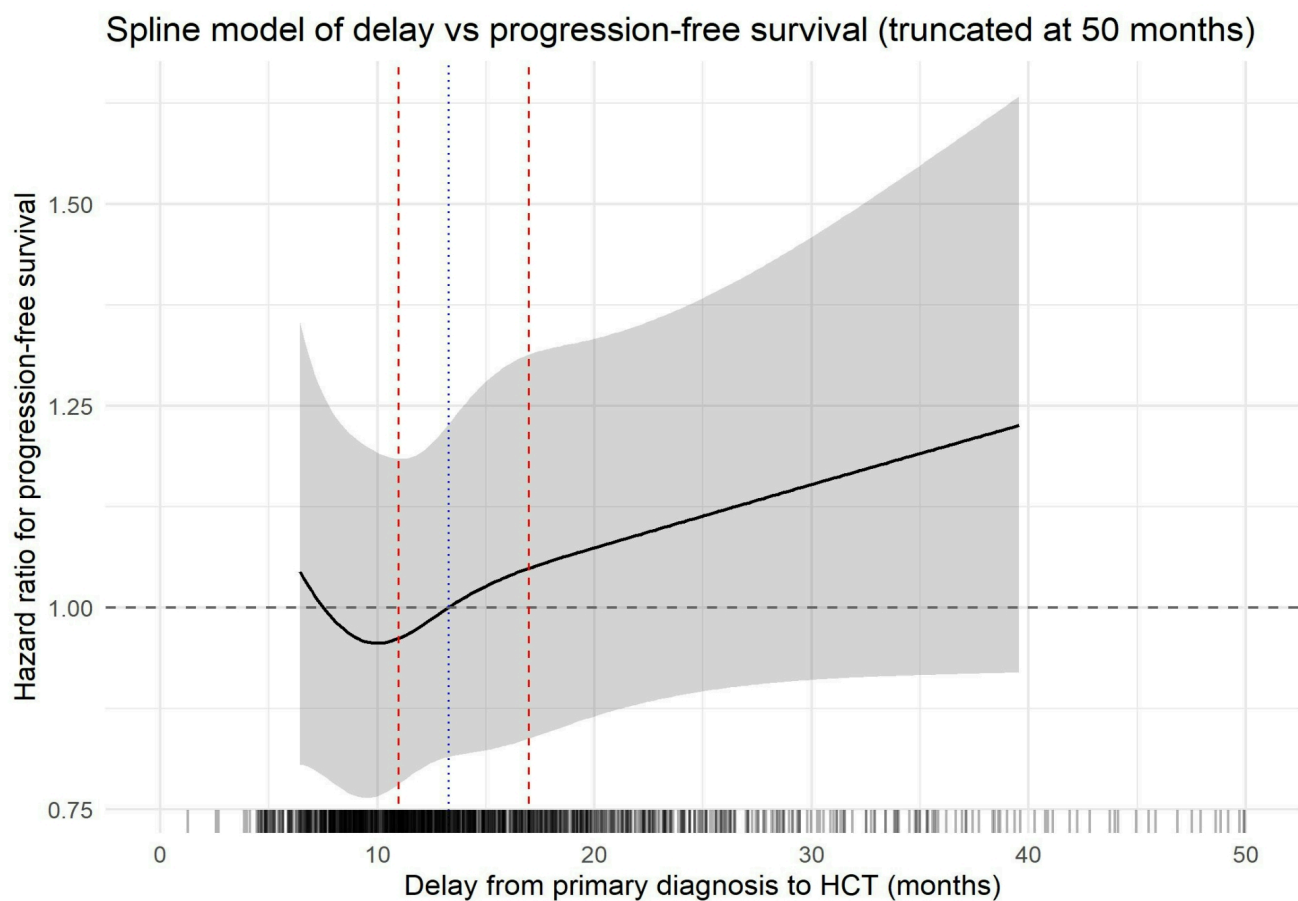


Figure 3

Adjusted spline model of the association between interval and relapse-free survival. Vertical dashed red lines mark the tertile cut-points of the interval distribution used in categorical analyses. Because very few patients had extremely long intervals, the curve is truncated at 50 months of interval; estimates beyond this range would be unstable.