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Implications of Selection Bias Due to Delayed Study Entry in Clinical Genomic Studies

Samantha Brown, MS, **Jessica A. Lavery, MS**, **Ronglai Shen, PhD**, **Axel S. Martin, MS**, **Kenneth L. Kehl, MD, MPH**, **Shawn M. Sweeney, PhD**, **Eva M. Lepisto, MA, MSc**, **Hira Rizvi, BA**, **Caroline G. McCarthy, MPH**, **Nikolaus Schultz, PhD**, **Jeremy L. Warner, MD, MS**, **Ben Ho Park, MD, PhD**, **Philippe L. Bedard, MD**, **Gregory J. Riely, MD, PhD**, **Deborah Schrag, MD MPH**, **Katherine S. Panageas, DrPH**, **AACR Project GENIE Consortium**

Memorial Sloan Kettering Cancer Center, New York, NY (SB, JAL, RS, ASM, HR, CGM, NS, GJR, KSP); Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA (KLK, EML, DS); Vanderbilt University Medical Center, Nashville, TN (JLW, BHP); Princess Margaret Cancer Centre, Toronto, ON (PLB), and the American Association for Cancer Research, Philadelphia, PA (SMS).

Understanding the predictive and prognostic effects of molecular aberrations in tumors has dramatically changed drug development and the practice of cancer medicine. Broader availability of tumor genomic data linked to treatment exposures and survival outcomes will propel further advances in precision oncology and translational research. However, rigorous analytic methods must be applied to ensure that inferences from observational data are valid. A key challenge that threatens the validity of interpretation of clinico-genomic data is the time lapse between molecular testing and diagnosis.

An underlying assumption of survival analysis is that study entry and time of origin are aligned. In clinico-genomic cohorts, the specific sampling is molecular tumor profiling and the origin time is often diagnosis or treatment initiation. Ideally, study samples (genomic profiling) would be obtained at the time origin of interest, but in clinical practice this is often not the case. Genomic sequencing is frequently performed months or even years following diagnosis. This delayed entry leads to left truncation, since all patients who had an event or were lost to follow-up prior to sequencing are not captured in the analysis. As a result, the data will be subject to length bias in a naïve analysis and will affect the validity of time-to-event analyses and accuracy of survival estimates.[1–4] To provide interpretable and reproducible analyses, it is imperative to apply appropriate statistical methods to these complex data.[2,5] Here we illustrate the consequences of ignoring left truncation and describe an approach to correct for length bias, in patients with stage IV colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) sourced from a large clinico-genomic database.

The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange Biopharma Collaborative (GENIE BPC) is an effort to supplement genomic profiles with comprehensive clinical ("phenomic") data from 50,000

Corresponding Author: Katherine S Panageas, Attending Biostatistician, Memorial Sloan Kettering Cancer Center, 485 Lexington Avenue, 2nd Floor York, NY 10017 (panageak@mskcc.org).

patients.[6] Clinical data are obtained from structured fields in electronic health records and tumor registries that contain information such as diagnosis and staging variables, cancer drug treatment start and stop dates and the laboratory values for tumor markers. Critical outcomes in oncology are typically not structured in electronic health records and are therefore ascertained by manual curation using a standardized framework. Using the PRISSMM phenomic data model, curators abstract unstructured text, including notes from the pathologist, radiologist and medical oncologist.[7] The resulting structured data will be publicly available to address diverse research questions and for analyses that include discovery, prediction of clinical phenotypes, and risk stratification.

Patients were selected for entry into the GENIE BPC study if they had genomic profiling performed within the years 2015–2017. For some patients, genomic profiling was performed shortly after diagnosis, but for others, genomic profiling was performed much later: the median time between diagnosis and genomic profiling was 6.25 months (IQR: 2.43, 19.33) and 2.34 months (IQR: 1.38, 7.83) for patients diagnosed with stage IV CRC (N=659) and stage IV NSCLC (N=727), respectively. To demonstrate the varying degrees of delayed entry, survival outcomes are estimated from two origin times, diagnosis and start of the most common first-line therapy. The most common first-line regimen was FOLFOX for stage IV CRC (N=285) and carboplatin/pemetrexed for stage IV NSCLC (N=137). In Figures 1a/c and 2a/c, each patient's survival time is indicated by a blue line with a black line overlaid to illustrate duration of delayed study entry. When the time of origin is cancer diagnosis, all patients in both cohorts were subject to left truncation, as their genomic sequencing occurred after their diagnosis date. For survival from the start of regimen, 95% of stage IV CRC patients who received FOLFOX and 76% of stage IV NSCLC patients on first-line carboplatin/pemetrexed as first-line therapy had sequencing performed after the start of regimen.

In the absence of left truncation, patients enter the risk set at the time of diagnosis (or start of regimen) and are followed until they experience an event or are censored; this results in a decreasing number of patients at risk over time. However, when data are left truncated, analyses must reflect that patients enter the risk set and begin being followed only at the time of genomic sequencing; otherwise, the presence of delayed study entry results in overestimation of the survival distributions.[8] Due to this staggered entry, the number of patients at risk does not consistently decrease over time, as illustrated in the risk tables (Figures 1b/d and 2b/d). The extent of bias is illustrated in the unadjusted and adjusted Kaplan Meier overall survival curves (Figures 1b/d and 2b/d). Accounting for delayed entry can be implemented in standard statistical software, such as using the *survfit* function in the R package *survival* or *PROC PHREG* in SAS software.[9–11] SAS and R code along with the corresponding de-identified stage IV CRC GENIE BPC data are provided in a supplemental GitHub repository (https://github.com/slb2240/delayed_entry_clin_genom_studies).

For each time origin of interest, we calculate the absolute difference in median OS from estimates that are adjusted and unadjusted for delayed entry. The extent of such differences is influenced by the delayed entry distribution and survival times. For both cohorts, the absolute differences in median OS from diagnosis after adjustment for left truncation were greater than one year in both cohorts (13.0 and 12.0 months in stage IV CRC and NSCLC, respectively), highlighting the extent to which interpretation of the data could be distorted. Similarly, the survival curves are shifted when evaluating OS from start of regimen, though the effect is attenuated.

Importantly, the survival estimates obtained after adjustment for delayed entry are consistent with established estimates from recent randomized clinical trials. Venook reported the results of a multi-center randomized trial of first line therapy with FOLFOX or FOLFIRI combined with either bevacizumab (N = 559) or cetuximab (N = 578) among patients with KRAS wild-type metastatic CRC.[12] Among patients who received chemotherapy with bevacizumab, median overall survival was 29.0 months with bevacizumab and 30.0 months with cetuximab. In GENIE BPC, 132 KRAS wild-type stage IV CRC patients received first-line FOLFOX/FOLFIRI with bevacizumab. For this group, who had similar sociodemographic and clinical characteristics as the trial participants, median OS was 25.8 months (95% CI: 20.8, 34.2) after adjustment for left truncation and 40.9 months (95% CI: 33.9, 49.2) without adjusting for delayed entry.

For lung cancer, survival outcomes were compared to those obtained from a randomized clinical trial recently reported by Ramalignam et al.[13] They compared first-line osimertinib (N = 279) or erlotinib/gefitinib (N = 277) among patients with EGFR-mutant advanced NSCLC, reporting median OS estimates of 38.6 months (95% CI: 34.5, 41.8) and 31.8 months (95% CI: 26.6, 36.0) among patients who received osimertinib and erlotinib/gefitinib, respectively. In the analogous cohort of EGFR-mutant stage IV NSCLC patients from GENIE BPC (N = 76), the median overall survival from first-line erlotinib/gefitinib when adjusted for left truncation was 31.2 months (95% CI: 25.0, 44.7) as opposed to 42.7 months (95% CI: 32.3, 50.3) when delayed entry was not accounted for. Although these informal group comparisons do not adjust for differences in the clinical and sociodemographic attributes of patients, these examples illustrate that the median survival estimates obtained without adjusting for delayed entry greatly exceed clinical trial-derived estimates and therefore strain credulity. Estimates obtained after adjustment for delayed entry more closely resemble the clinical trial derived estimates.

As genomic sequencing at diagnosis is not standard across institutions, delayed study entry is expected to persist and is an issue that researchers must attend to in evaluating clinico-genomic analyses. Some have taken the approach of restricting analyses to patients who are not left truncated, but this greatly reduces available sample size and introduces other selection biases. For example, while Medicare now covers broad genomic testing for all stage IV solid tumor patients, uninsured or underinsured patients may not have similar access and would not be expected to have genomic testing concurrent with diagnosis. Instead, including all patients with genomic sequencing and making adjustment for left truncation standard practice for survival analyses in studies with delayed entry is the preferred approach, just as accounting for right censoring is standard in time to event analyses.[8] When estimating hazard ratios from a Cox proportional hazards model, we must also adjust for left truncation to obtain consistent regression coefficient estimators and to account for possible differential left truncation across levels of covariates. Regression techniques exist under left truncation and length-biased data.[8,14,15]

It is important to note that adjusting for left truncation is not a panacea. The approach described here relies on the assumption that the survival and truncation times are independent. Dependent left truncation occurs when clinical worsening prompts genomic sequencing and thus cohort entry is correlated with prognosis.[16] Kendall's tau statistic or regression methods may be applied to assess whether there is dependent left truncation.[17–20] If there is evidence of dependency, then an alternative statistical method may be necessary.[21,22]

Building large-scale clinico-genomic datasets requires standardized implementation across many institutions. Specifying inclusion criteria based on genomic sequencing at the design or data collection stage is a streamlined approach that can be operationalized uniformly. These data are a valuable resource for evaluation of real-world cancer outcomes and should be analyzed using appropriate methods to maximize their potential. Analysts must become adept at application of appropriate statistical methods to ensure valid, meaningful, and generalizable research findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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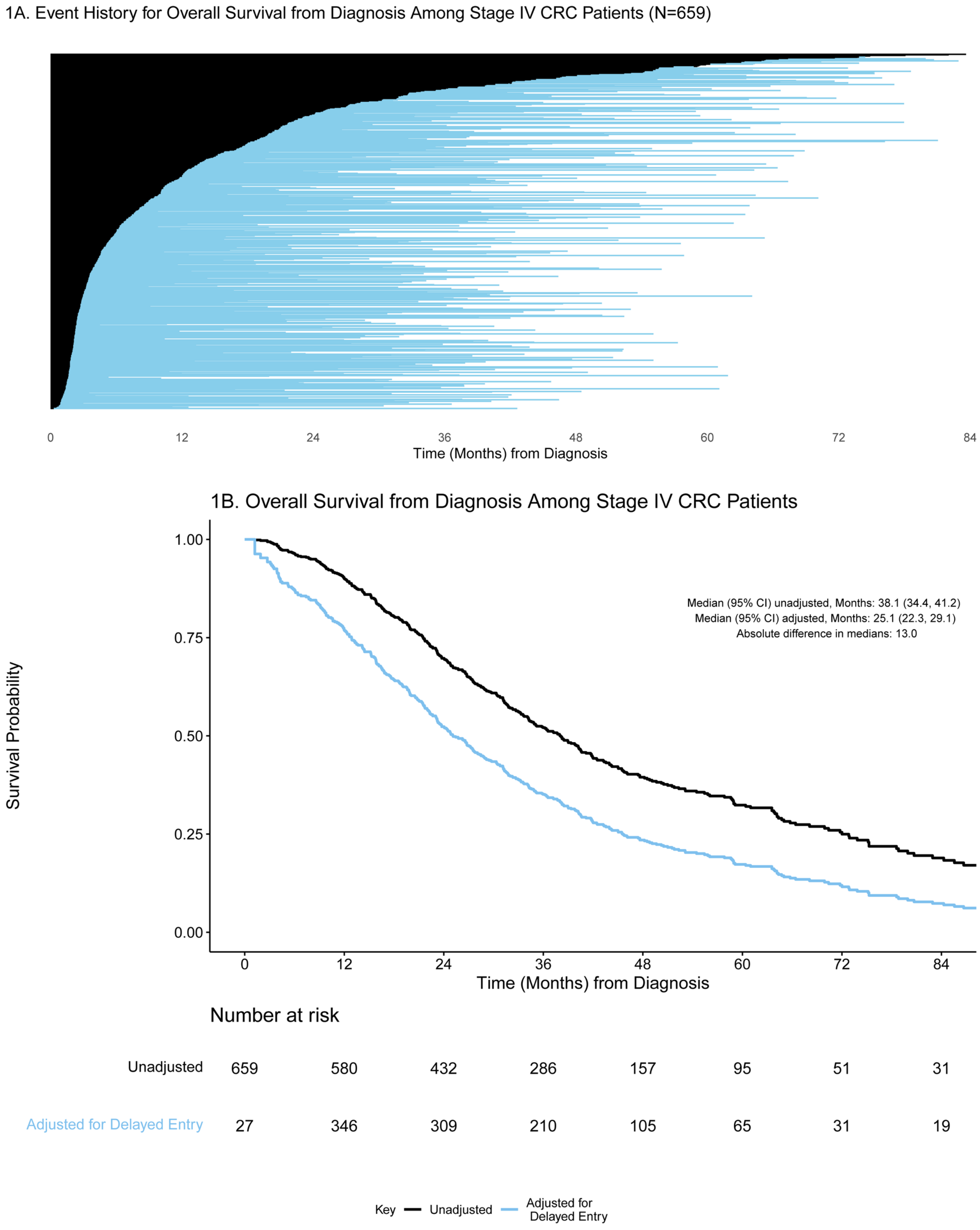
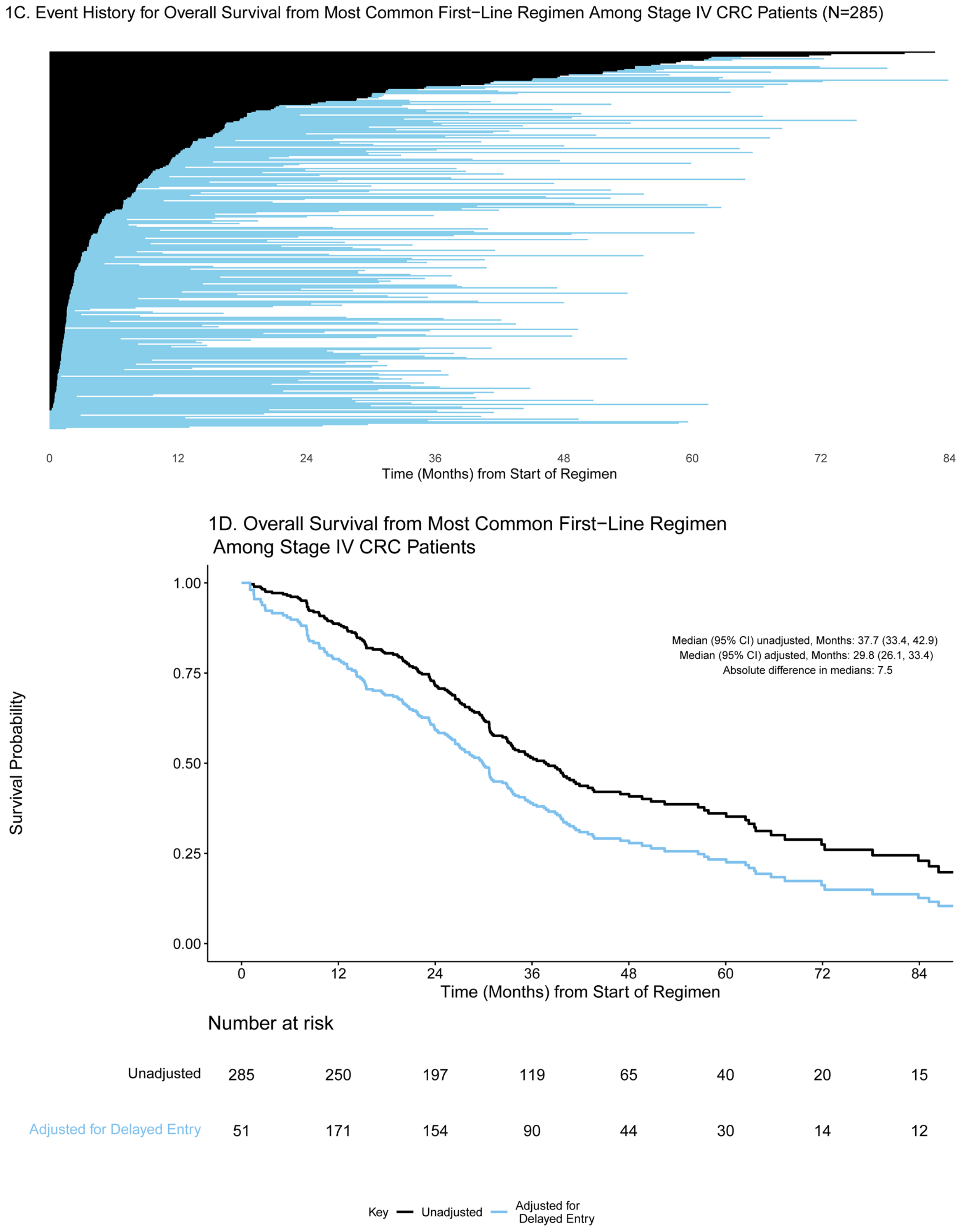


1A. Event History for Overall Survival from Diagnosis Among Stage IV CRC Patients (N=659)

1B. Overall Survival from Diagnosis Among Stage IV CRC Patients

Number at risk

Unadjusted	659	580	432	286	157	95	51	31
Adjusted for Delayed Entry	27	346	309	210	105	65	31	19



1C. Event History for Overall Survival from Most Common First−Line Regimen Among Stage IV CRC Patients (N=285)

1D. Overall Survival from Most Common First−Line Regimen Among Stage IV CRC Patients

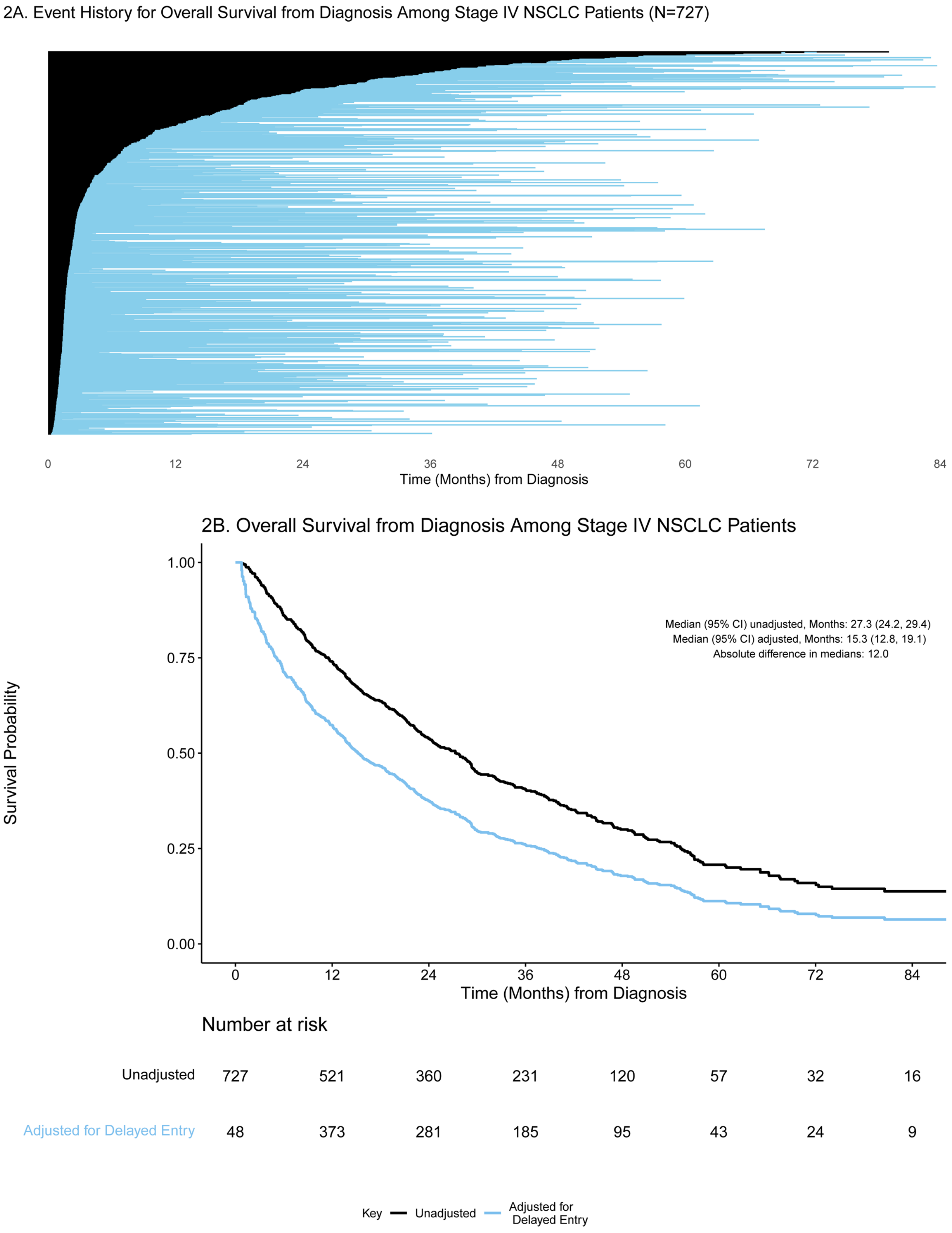
Median (95% CI) unadjusted, Months: 37.7 (33.4, 42.9)
Median (95% CI) adjusted, Months: 29.8 (26.1, 33.4)
Absolute difference in medians: 7.5

Number at risk

Unadjusted	285	250	197	119	65	40	20	15
Adjusted for Delayed Entry	51	171	154	90	44	30	14	12

Figure 1:

A) Event history for overall survival from diagnosis among stage IV CRC patients (N=659). Each patient’s survival time from diagnosis is indicated by a blue line with a black line overlaid to illustrate duration of delayed study entry. B) Kaplan-Meier curves illustrating overall survival from diagnosis among stage IV CRC patients with and without adjustment for delayed study entry. C) Event history for overall survival from most common first-line regimen among stage IV CRC patients (N=285). Each patient’s survival time from start of regimen is indicated by a blue line with a black line overlaid to illustrate duration of delayed study entry. D) Kaplan-Meier curves illustrating overall survival from start of most common first-line regimen among stage IV CRC patients with and without adjustment for delayed study entry.



2A. Event History for Overall Survival from Diagnosis Among Stage IV NSCLC Patients (N=727)

2B. Overall Survival from Diagnosis Among Stage IV NSCLC Patients

Number at risk

	0	12	24	36	48	60	72	84
Unadjusted	727	521	360	231	120	57	32	16
Adjusted for Delayed Entry	48	373	281	185	95	43	24	9

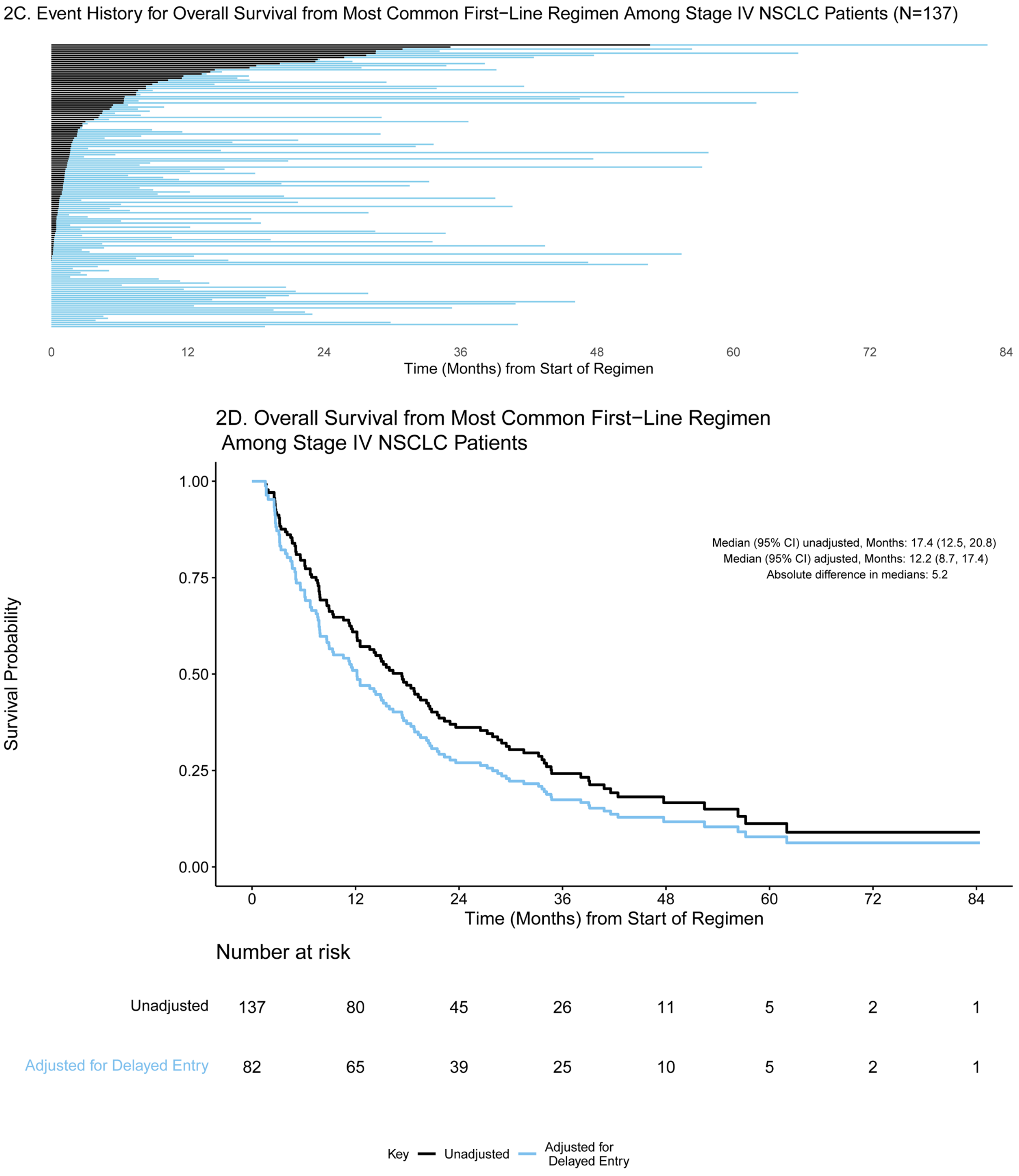


Figure 2:

A) Event history for overall survival from diagnosis among stage IV NSCLC patients (N=727). Each patient's survival time from diagnosis is indicated by a blue line with a black line overlaid to illustrate duration of delayed study entry. B) Kaplan-Meier curves illustrating overall survival from diagnosis among stage IV NSCLC patients with and without adjustment for delayed study entry. C) Event history for overall survival from most common first-line regimen among stage IV NSCLC patients (N=137). Each patient's survival time from start of regimen is indicated by a blue line with a black line overlaid to illustrate duration of delayed study entry. D) Kaplan-Meier curves illustrating overall survival from start of most common first-line regimen among stage IV NSCLC patients with and without adjustment for delayed study entry.