RE:
Abou-Jawde *et al*. The role of race, socioeconomic status, and distance traveled on the outcome of African-American patients with multiple myeloma. Haematologica 2006; 91: 1410-3

A recent study by Abou-Jawde et al. evaluated the role of race, socioeconomic status (SES), and distance traveled on the survival of multiple myeloma (MM) patients.[1] The authors reported that race, SES, and distance traveled were not of prognostic importance for MM and that African-Americans (AAs) and Caucasians (CAs) treated at a dedicated multidisciplinary myeloma clinic had similar survival.[1p.1412] We commend the authors for addressing neglected issues regarding MM. However, methodologic limitations produced questionable findings. Previous studies have suggested a strong correlation between race and SES with outcome for a variety of disorders.[2] Distance traveled may be a function of race and SES, which collectively serve as proxies for an underlying causal mechanism. The authors simultaneously evaluated the effect of all three variables in a proportional hazard model.[1p.1411] Simultaneous analysis of correlated variables potentially over-controlled for the underlying mechanism and thus reduced the ability to observe separate effects of race, SES, and distance traveled. It would have been more congruent with the study objectives to stratify by race and separately investigate SES or distance traveled. The authors also over-controlled for correlated clinical prognostic factors and omitted other important potential confounders. MM stage was defined by the Southwest Oncology Group (SWOG) staging system and incorporated into the model as a covariate along with $\beta 2$ microglobulin ($\beta 2M$) and albumin.[1p.1411] However, SWOG already incorporates $\beta 2M$ and albumin as part of its staging criteria.[3] The results suggest over-controlling because stage, $\beta 2M$, and albumin were not reported as predictors of MM survival,[1p.1411] despite ample evidence to the contrary.[3-5] Furthermore, important prognostic factors such as C-reactive protein (CRP) were not addressed, despite evidence that concurrently elevated CRP and $\beta 2M$ are markers of poor prognosis in MM.[4] Elevated lactate dehydrogenase (LDH) is another important marker of poor survival for MM patients that was not incorporated.[4] Inclusion of LDH could have partially accounted for lack of cytogenetic data.[4] Disease status and treatment received were other potential confounders that were not controlled. The inclusion of relapsed patients was a fundamental source of misclassification bias. Relapsed CAs represented 45% of all CAs and relapsed AAs represented 37% of all AAs.[1p.1411] Person-time survival data prior to relapse was not included for patients categorized as relapsed MM at the start of follow-up. Relapsed disease status may represent patients that completed a full course of treatment at other institutions prior to admission at Cleveland Clinic. Consequently, survival among relapsed patients may be highly underestimated compared to newly diagnosed patients. The magnitude of misclassification could have accounted for negative findings, even if race were an important prognostic factor.

Inappropriately defined exposure and outcome were also sources of misclassification bias. SES was a crudely measured exposure derived from ecologic data by zip codes, whereas other variables were individual-level. Furthermore, a consistent definition of survival is not used throughout the analysis. The authors equate loss-to-follow-up with death in Figure 2,[1p.1412] despite clearly different implications. The authors utilized Cox proportional hazard regression *to investigate the effects of interest*,[1p.1411] but did not report a measure of effect such as a hazard ratio. Hazard ratios are vital estimates for interpreting results because the model assumes that hazard rate, not survival time, is a function of the independent variables.[6p.473] Rather, the authors based their conclusions on incorrect assumptions and an inadequately powered, p-value driven, uncontrolled log-rank test.[1p.1412] Log-rank tests are inappropriate for detecting differences if survival curves overlap.[7] A fundamental assumption of the log-rank test and Cox proportional hazard regression is that survival probabilities (hazards) are constant.[8] However, as previously mentioned, survival probabilities are unlikely to be equivalent for relapsed and newly diagnosed patients. Furthermore, log-rank tests do not allow adjustment for potential confounders.[8] Ultimately, the study was inadequately powered to observe an association even if race were a prognostic factor because the sample included only 38 total AAs, of whom only 24 were newly diagnosed. Lack of power is illustrated by the clinically significant two-fold difference of median survival time for AAs compared to CAs (64 vs. 32 months, respectively). A combination of inappropriate variable selection, misclassification bias, improper analyses, and inadequate power preclude valid inferences from the study by Abou-Jawde et al.[1] The study illustrates an unsettling trend of methodologic abandonment that may contribute to persistent etiologic inconsistencies evident among epidemiologic investigations of MM. Future studies should employ valid epidemiologic methods for design, conduct, and analysis.

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References

1. Abou-Jawde RM, Baz R, Walker E, Choueiri TK, Karam MA, Reed J, Faiman B, Hussein M. The role of race, socioeconomic status, and distance traveled on the outcome of African-American patients with multiple myeloma. Haematologica 2006; 91: 1410-1413.
2. LaVeist TA. Disentangling race and socioeconomic status: a key to understanding health inequalities. J Urban Health 2005 Jun;82(2 Suppl 3):iii26-34.
3. Jacobson JL, Hussein MA, Barlogie B, Durie BG, Crowley JJ; Southwest Oncology Group. A new staging system for multiple myeloma patients based on the Southwest Oncology Group (SWOG) experience. Br J Haematol 2003 Aug;122(3):441-50.
4. Angtuaco EJ, Fassas AB, Walker R, Sethi R, Barlogie B. Multiple myeloma: clinical review and diagnostic imaging. Radiology 2004 Apr;231(1):11-23.
5. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, *et al*. International staging system for multiple myeloma. J Clin Oncol 2005 May 20;23(15):3412-20.
6. Lewicki P, Hill T. Statistics: Methods and Applications. Tulsa, OK. Statsoft; 2006.
7. Bland JM, Altman DG. The log-rank test. BMJ 2004;328:1073
8. Bewick V, Cheek L, Ball J. Statistics review 12: Survival analysis. Crit Care 2004; 8(5): 389–394.