Predictors of Reduced Survival for Adult-diagnosed Cystic Fibrosis: Older Age at Diagnosis, a Substitute for Older Age?

To the Editor:

In their study, Desai and colleagues identified clinical predictors of reduced lung-transplant-free survival in patients with adult-diagnosed cystic fibrosis (1). Older age at diagnosis (hazard ratio, 1.24 for a 5-year higher age at diagnosis) was mentioned as an important risk factor, in addition to diabetes and lung function at baseline. This finding was based on a multivariable Cox regression, using years since diagnosis as the time variable. However, by choosing years since diagnosis, the finding for age at diagnosis might merely reflect the trivial fact that older patients have a higher risk of dying. Consider, for example, two patients (A and B) being diagnosed at 20 and 25 years, respectively, and having identical values for all other covariates considered in their multivariable model. Then, 10 years after diagnosis, patient B’s hazard ratio is 1.24 higher than patient A’s hazard ratio. But this is not so surprising, as patient B is at that moment 5 years older (patient A, aged 30 yr; patient B, aged 35 yr). Redoing the analysis with age instead of years since diagnosis can reveal whether or not labeling older age at diagnosis as a risk factor results from this possible artifact.

Reply: Predictors of Reduced Survival for Adult-diagnosed Cystic Fibrosis: Older Age at Diagnosis, a Substitute for Older Age?

From the Authors:

We thank Fieuws and colleagues for raising this important point regarding the timescale applied in our study (1). Our analysis showed that age at diagnosis is a predictor of lung-transplant-free survival. However, as Fieuws and colleagues have highlighted, this is not surprising, as those individuals diagnosed late are older and inherently at a higher risk for mortality, which is a possible artifact of strong age effects.

As recommended by Fieuws and colleagues, we have redone the analysis, using age as the timescale. The association with diabetes (hazard ratio [HR], 3.69, 95% confidence interval [CI], 1.21–11.26) and lung function (HR, 1.36 per 5% decrease in forced expiratory volume in 1 s percentage predicted; 95% CI, 1.24–1.50) remained unchanged, but the association between age at diagnosis and survival is now reversed (HR, 0.58 per 5-yr increase; 95% CI, 0.39–0.86). This suggests that older age at diagnosis is protective of our outcome as an indicator of less aggressive CF disease.

Unfortunately, this analysis also carries a built-in selection bias, as


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Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reference


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individuals diagnosed at an older age must live to that age to be diagnosed and included in the cystic fibrosis registry, which leads to an "immortal" survival time bias.

The relationship between age at diagnosis and survival is complex and must be interpreted with caution, as noted by Fieuws and colleagues. Although older age at diagnosis inherently increases the risk for death because of age effects, older age at diagnosis may also reflect milder disease and reduced risk for death. However, being diagnosed later in life also means there were additional years of untreated cystic fibrosis, which could result in a negative effect on health and, hence, result in an increased risk for death. We again thank Fieuws and colleagues for bringing attention to this important issue and for highlighting that older age at diagnosis may not necessarily be a risk factor for worse outcomes in adult-diagnosed cystic fibrosis, a message we would not want miscommunicated to patients.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Toward Enhancing the Rigor of Causal-Inference Studies

To the Editor:

In an apparently unprecedented and praiseworthy move (1), 47 editors of 35 medical journals recently published a guidance document on “the design and reporting of observational causal inference studies” (2). The eminent group of authors was motivated by a “call for increased rigor in observational research methods,” but unfortunately the rigor-promoting document itself contains some confusing or untenable ideas, in my opinion.

First, two of the “questions about etiology” provided by the authors for illustrating why they “use causal inference” are actually not about etiology, with the misrepresentation of this concept apparently stemming from the failure to distinguish the etiologic versus interventional genres of causality in medicine (3). Another consequence of this failure is the authors’ encouragement to design observational studies by emulating clinical trials, even if these trials represent an ill-chosen paradigm for etiologic research (3).

Second, the authors “make a distinction between causal inference and prediction modeling,” but in medicine, thinking of a person’s future course of health requires consideration of potential adoption of particular interventions and/or lifestyles that might be reasonable to consider in any given situation—and ipso facto, it requires consideration of the magnitude of anticipated effects of these actions (4). Thus, the topic at issue here is both “predictive” (i.e., prognostic) and causal, so when assessing, for example, a person’s risk of developing lung cancer, it would be important to consider the person’s anticipated cigarette-smoking–related behavior, as the risk depends—causally—on it (5). And another upshot of this is that clinical trials (and their nonexperimental counterparts) should be seen as causal-prognostic studies.

Third, according to the authors’ description of the “historical approach to defining a confounder,” a confounder must be “a cause of the outcome of interest,” whereas the association of the confounder with the exposure at issue is strictly a matter of “prior knowledge.” However, I believe that in the “historical,” pre-directed-acyclic-graph–era conception, a confounder can be a noncausal determinant of the outcome’s occurrence, whereas the exposure–confounder association is viewed as an ad hoc, study-base–specific matter.

Fourth, in reference to the scenario depicted in Figure 1C (2), the authors state that “controlling for a collider will open the backdoor path, thereby introducing confounding,” but I do not believe this view accords with the proper conception of confounding (whether it be considered from the historical or modern vantage).

Fifth, according to the authors, “it is reasonable to use the label ‘causal association’...to describe findings arising from an observational study,” but a causal association is not something that can be found and described in a study, as causality is unobservable.

Sixth, I found it puzzling that in reference to the example illustrating their recommended way of reporting study results (2, p. 27), the authors characterize the “effect estimate” as “imprecise,” while characterizing the “point and interval estimates” of the effect as “informative” (with this apparent incoherence highlighting the fact that “precise vs. imprecise”—like “informative vs. noninformative” and “significant vs. nonsignificant”—is an arbitrary and subjective dichotomy.) Furthermore, the authors’ interpretation of the upper