To the Editor:

The frequently unsatisfactory outcome following standard therapies in acute myeloid leukemia (AML) has led pharmaceutical companies to develop many new drugs, which are tested in “clinical trials.” Their underpinning is patients’ reasoning the benefit/risk ratio with the trial is higher than with the standard.1,2 However, trials typically have strict eligibility criteria, thus excluding many patients. For example, serum bilirubin often has to be < 1.5 to 2.0 mg/dL and glomerular filtration rate (GFR) > 60 mL/min.3 4 This is the case for bilirubin even if a new drug is known not to be excreted by the liver and likewise for creatinine/GFR and the kidney.3,4 Another rationale for exclusion might be the possibility that abnormal renal or hepatic function will indirectly indicate a predisposition to treatment-related mortality (TRM). Here we explore this possibility.

We included 984 adults with newly-diagnosed or relapsed/refractory AML given “intensive chemotherapy” at our center from 1999 to 2017. Intensive chemotherapy denoted 7 + 3 or regimens containing cytarabine at 1 to 2 g/m2 daily × 4 to 5 days combined with mitoxantrone and cladribine (GCLM), clofarabine (GCLAC), or standard regimens like MEC (mitoxantrone, etoposide, and cytarabine) or FLAG-IDA (fludarabine, cytarabine, idarubicin, and granulocyte-colony stimulating factor). The most commonly used treatments for newly-diagnosed AML were 7 + 3 (49%), GCLAM (32%), and GCLAC (10%). For relapsed/refractory (R/R) AML, 39% received GCLAM, 18% GCLAC, 18% MEC, and 16% 7 + 3.

TRM was defined as death within 28 days of treatment initiation,7,8 based on observations that death rates declined sharply after these 4 weeks, suggesting that patients dying during these 4 weeks comprised a distinctive group. However, we also evaluated death within 56 days as a sensitivity analysis. We evaluated association between TRM and pre-treatment glomerular filtration rate (GFR), calculated based on the Modification of Diet in Renal Disease equation, which accounts for age, gender, race, and creatinine levels and serum total bilirubin.9,10 We also included those covariates comprising the TRM score: age, ECOG PS (0-1 vs. 2-4), de novo versus secondary AML, serum albumin, white blood cell count and platelet count, R/R versus newly-diagnosed AML, 7 + 3 versus other therapies (with cytarabine at doses of at least 1 g/m2), and year treatment started (1999-2009 vs. 2010-2017).7 ECOG PS was assessed prospectively in about 25% of cases and retrospectively in 75%. GFR was considered low if < 60 mL/min and serum bilirubin high if > 1.5 mg/dL; our center’s upper limit of normal is 1.5 mg/dL. We compared TRM between patients with GFR < 60 mL/min and total bilirubin ≥ 1.5 versus > 1.5 mg/dL, with univariate and multivariable logistic regression models. The multivariable model was developed using backward selection with 5-fold cross validation used to estimate area under receiver operating characteristic curves (AUC) for TRM. AUCs of 0.6 to 0.7, 0.7 to 0.8, and 0.8 to 0.9 indicate poor, fair, and good predictive ability, respectively7,8; these AUCs, rather than P-values (which were not adjusted for multiple comparisons), form our principal vehicle for inference. All analyses were performed using R (http://www.r-project.org). This study was approved by our Institutional Review Board.

One hundred sixty-one (18%) of 876 patients in whom GFR was assessed had GFR < 60 mL/min (low), including 112 patients with GFR 45 to 59 mL/min, 39 with GFR 30 to 44 mL/min, and 10 with GFR < 30 mL/min. The low GFR group was older than the normal GFR group (median, 62 vs. 56 years), more often had ECOG PS 2 to 4 (25.5% vs. 18.2%), and had a higher TRM rate (10% vs. 5%, rising to 12% if GFR < 45 mL/min) and day 56 mortality rate (16% vs. 9%). The odds ratio of TRM with normal GFR versus low GFR was 0.46 (95% confidence interval,
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0.24-0.86; \( P = .02 \). Eighty-one (8%) of 959 patients had bilirubin > 1.5 mg/dL (high). There was no difference in median age, but ECOG PS was 2 to 4 in 17.1% and 35.8%, and TRM rates were 4% and 15% in the normal and elevated bilirubin groups, respectively (14% TRM if bilirubin > 2.0 mg/dL). The odds ratio for TRM of high bilirubin compared with normal bilirubin was 3.84 (95% confidence interval, 1.92-7.96; \( P < .001 \)). The 56-day mortality was 24.7% and 8.1% for high and normal bilirubin, respectively. There was no statistical difference in either 28- or 56-day mortality when comparing patients with direct or indirect predominant hyperbilirubinemia.

Despite these “statistically significant” \( P \)-values, the AUCs values for low GFR (< 60 mL/min) and for high bilirubin (> 1.5 mg/dL) were only 0.57 and 0.58, respectively. These relatively low AUC values remained in multivariable analyses. Thus, when considering low GFR together with the covariates previously found associated with TRM (see above) and R/R versus newly-diagnosed AML, age, performance status, secondary AML, R/R disease, low GFR, albumin, and therapy were selected. The AUC of the multivariable model was 0.64. In the model with bilirubin, age, ECOG PS, secondary AML, R/R disease, albumin, therapy, and year treatment started, but not bilirubin, were selected for the multivariable model. The AUC of this model was 0.67. Conclusions were the same using 56-day mortality. In particular, although low GFR was significantly associated with TRM in both univariate and multivariable models, the AUC of the multivariate model was 0.64, and bilirubin was not selected as a covariate in a multivariable model.

Exclusion of patients from clinical trials makes it impossible to know how an excluded patient might have fared had he/she been included, a question of relevance particularly once a drug receives regulatory body approval. Furthermore, an ethical issue may arise when patients with poor prognoses with standard therapy are excluded from trials of what are often heralded as potentially promising therapies. Under these circumstances, reasons for exclusion should, as far as possible, be based on data rather than habit. Thus, excluding patients with abnormal bilirubin or GFR would be sensible if the liver or kidney involved in metabolism/excretion of the drug studied in the trial. However, data from Statler et al suggest this is frequently not the case.3,4 Another compelling reason for exclusion would be an explicit connection between the exclusion criteria and risk of TRM. Prior multivariable models examining TRM have found pre-treatment creatinine, but not bilirubin, is predictive of TRM.5 Exclusion might also be based on the risk of grade 3 to 4 renal or hepatic toxicity, but Veatch et al showed that this was not related to increase in TRM.6 Here, we re-examined this question using GFR, widely accepted as a better measure of renal function than creatinine.9,10

Our principal finding is that neither GFR nor serum bilirubin strongly predicted TRM in AML. Seventy percent of patients with GFR < 60 mL/min had relatively mild decreases in GFR (45-59 mL/min), but TRM did not differ substantially (12% vs. 10%) according to GFR 45 to 59 mL/min versus < 45 mL/min. Our data are consistent with data in patients receiving reduced intensity allogeneic hematopoietic cell transplant where GFR < 60 mL/min did not affect non-relapse mortality.12 Likewise, 55% of our patients with high bilirubin (> 1.5 mg/dL) had only mild elevations (1.6-2.0 mg/dL), but TRM was similar in the 1.6 to 2.0 mg/dL (\( n = 45 \)) and > 2.0 mg/dL (\( n = 36 \)) groups. A possible explanation for our results could be dose reduction in patients with low GFR or high bilirubin. However, this only occurred in 24 (14%) of 160 patients in the low GFR group, and in 16 (23%) of 70 patients in the elevated bilirubin group.

Readers might be surprised at the poor predictive ability of the multivariable models described here (AUCs, 0.64 and 0.67) particularly when contrasted with an AUC of 0.82 in our original paper evaluating prediction of TRM. Possible explanations are (1) the lower rates of TRM in the current population (5%-6%) than in the original paper (10%), likely reflecting that most of the current patients were treated in later years, by which time TRM rates had declined,13 and (2) the greater number of patients incurring TRM in the older study could lead to more precise and accurate models.

Our data are consistent with those from other studies that did not show worse outcomes in patients not eligible for clinical trials.14,15 However, even accepting that low GFR or high bilirubin may be associated with higher TRM rates, our data suggest such associations are relatively weak. Medicine is fundamentally concerned with considerations of benefit as well as risk. It is quite plausible that many patients with poor prognosis AML would be willing to accept small increments in TRM consequent to low GFR or high bilirubin in exchange for the more effective therapy promised by clinical trials, recalling that the disease, not its treatment, is the main cause of death in AML. Although this promise is often not borne out, this cannot be known a priori. In contrast, the typically unsatisfactory results with standard therapies are all too obvious. Under these circumstances, we suggest reconsideration of current conventions habitually excluding patients with GFR < 60 mL/min or serum bilirubin > 1.5 to 2.0 mg/dL from clinical trials. Exceptions might be in cases in which a new drug is excreted by the kidney (liver) and the patient has low GFR (high bilirubin), although here again benefit/risk considerations might suggest dose reductions rather than complete exclusion of patients.

References


