Original Article

Pre- and on-treatment lactate dehydrogenase as a prognostic and predictive biomarker in advanced non–small cell lung cancer

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BACKGROUND: The survival outcomes of patients with advanced non–small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs) are variable. This study investigated whether pre- and on-treatment lactate dehydrogenase (LDH) could better prognosticate and select patients for ICI therapy. **METHODS:** Using data from the POPLAR and OAK trials of atezolizumab versus docetaxel in previously treated advanced NSCLC, the authors assessed the prognostic and predictive value of pretreatment LDH (less than or equal to vs greater than the upper limit of normal). They further examined changes in on-treatment LDH by performing landmark analyses and estimated overall survival (OS) distributions according to the LDH level stratified by the response category (complete response [CR]/partial response [PR] vs stable disease [SD]). They repeated pretreatment analyses in subgroups defined by the programmed death ligand 1 (PD-L1) status. **RESULTS:** This study included 1327 patients with available pretreatment LDH. Elevated pretreatment LDH was associated with an adverse prognosis regardless of treatment (hazard ratio [HR] for atezolizumab OS, 1.49; $P = .0001$; HR for docetaxel OS, 1.30; $P = .004$; P for treatment by LDH interaction = .28). Findings for elevated pretreatment LDH were similar for patients with positive PD-L1 expression treated with atezolizumab. Persistently elevated on-treatment LDH was associated with a 1.3- to 2.8-fold increased risk of death at weeks 6, 12, 18, and 24 regardless of treatment. Elevated LDH at 6 weeks was associated with significantly shorter OS regardless of radiological response (HR for CR/PR, 2.10; $P = .04$; HR for SD, 1.50; $P < .01$), with similar findings observed at 12 weeks. **CONCLUSIONS:** In previously treated advanced NSCLC, elevated pretreatment LDH is an independent adverse prognostic marker. There is no evidence that pretreatment LDH predicts ICI benefit. Persistently elevated on-treatment LDH is associated with worse OS despite radiologic response. ***Cancer* 2022;128:1574-1583**.

KEYWORDS: advanced lung cancer, biomarker, lactate dehydrogenase (LDH), prognosis, predictive.

INTRODUCTION

Despite evidence of improved outcomes for patients treated with immune checkpoint inhibitors (ICIs) in advanced non–small cell lung cancer (NSCLC), there is significant variability in progression-free survival (PFS) and overall survival (OS).[1-6] For example, among patients with advanced NSCLC treated with ICIs in second- or later-line settings, approximately 1 in 2 progress within 3 months, but 1 in 5 remain progression-free beyond 1 year.[1-4] Programmed death ligand 1 (PD-L1) expression in tumors is used to guide selection for ICI therapy, particularly in the first-line setting, but this has its limitations.[7] Approximately 15% of patients with PD-L1–negative tumors[3,4] will derive a clinical benefit, whereas at least 40% of patients with PD-L1–positive tumors[3-5] will not. Therefore, there is a critical need for additional pre- and/or on-treatment biomarkers to better prognosticate, select, and predict the durability of benefit for patients with NSCLC treated with ICI therapy to inform treatment decisions and patient counselling.

Lactate dehydrogenase (LDH) is widely accepted as a prognostic marker in a range of advanced solid tumors, including NSCLC.[8-10] As a marker of systemic inflammation and tumor burden, LDH can modulate the tumor

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microenvironment by increasing the production of lactate and promoting immunosuppression.[11,12] For NSCLC, LDH and other inflammatory markers have been incorporated into prognostic models to risk-stratify patients treated with chemotherapy[9] and ICIs.[13] Mezquita et al[13] reported that elevated pretreatment LDH is associated with worse outcomes in patients treated with ICIs but not chemotherapy, and this suggests a potential role for treatment selection. However, the existing evidence is largely derived from retrospective studies with limited information on the PD-L1 status.[9,13,14] The prognostic and predictive value of LDH is best examined in randomized controlled trials (RCTs) of ICIs versus chemotherapy, which allow for analyses of comparative differences between treatment arms according to LDH levels.

In addition, for patients receiving ICIs for advanced NSCLC, very little is known about the clinical value of changes in LDH. The majority of prognostic risk tools[9,13] using LDH rely on baseline factors and do not assess the impact of its change with systemic therapy. Because LDH has the advantage of being cheap and accessible for serial sampling, it is worthwhile to evaluate whether dynamic changes in LDH relative to the baseline provide additional prognostic information.

To address these gaps, we used data from the POPLAR[2] and OAK[1] RCTs to assess both the pre- and on-treatment value of LDH in patients with advanced NSCLC after the commencement of ICIs or chemotherapy.

MATERIALS AND METHODS

Study Population

We used individual patient data from 2 trials of patients with previously treated NSCLC randomized to atezolizumab or docetaxel: the phase 2 trial POPLAR (NCT01903993)[2] and the phase 3 trial OAK (NCT02008227).[1] OS was the primary end point in both studies, and PFS was a secondary end point. Patients were assigned to atezolizumab (a 1200-mg fixed dose) or docetaxel (75 mg/m^2) every 3 weeks until there was Response Evaluation Criteria in Solid Tumors–defined progressive disease, there was unacceptable toxicity, or the investigator deemed that the patient no longer derived benefit from treatment. Both POPLAR and OAK showed similar PFS with atezolizumab in comparison with docetaxel, but there was a significant OS benefit. Full details have been previously reported.[1,2] For our analysis, patients with known *EGFR* mutations and *EML4-ALK* translocations were excluded because ICIs were considered to be less effective in these patients.[15]

Pre- and On-Treatment LDH

LDH was measured in local laboratories before study commencement and then at the start of each treatment cycle. We evaluated pretreatment LDH as a continuous and categorical variable on the basis of the local laboratory cut point of the upper limit of normal (ULN) to better reflect how it might be used in routine practice.

Statistical Analysis

Pretreatment LDH

We summarized baseline patient data descriptively. We examined the prognostic value curves for PFS and OS outcomes, which were compared with the log-rank test, and performed univariate analyses with Cox proportional hazards regression modeling. To assess whether LDH was an independent prognostic factor, a multivariate Cox model was fitted with variables selected according to their clinical relevance and statistical significance in the univariate analyses (cutoff $P < .20$). The baseline variables considered included the following: treatment arm; sex; Eastern Cooperative Oncology Group performance (ECOG) status; smoking status; LDH; histology; PD-L1 status; and presence of liver, bone, and brain metastases. To assess whether LDH was predictive of treatment efficacy, a Cox model with a treatment covariate (atezolizumab vs docetaxel), the LDH status, and their interaction was used.

On-treatment LDH

We examined on-treatment LDH by summarizing changes in LDH relative to the baseline as follows: 1) remain high (LDH > ULN), 2) remain low (LDH ≤ ULN), 3) high to low (LDH > ULN at the baseline but LDH ≤ ULN after the baseline), and 4) low to high (LDH ≤ ULN at the baseline but LDH > ULN after the baseline). We evaluated the prognostic value of on-treatment LDH by correlating the LDH level (≤ULN vs >ULN) with PFS and OS at different landmark time points (6, 12, 18, and 24 weeks) for each treatment arm; we excluded those patients who progressed or died before landmark time points. Because only a minority of patients experienced an LDH change (from high to low or from low to high), we assessed on-treatment changes in LDH by using landmark analyses at week 6 for both treatment arms.

To assess whether an LDH change at 6 weeks was associated with a clinical benefit (complete response [CR], partial response [PR], or stable disease [SD]) at 12 weeks, we performed a logistic regression analysis. To further assess the additive value of LDH over the Response Evaluation Criteria in Solid Tumors response, we estimated distributions of PFS and OS according to LDH

levels among those with CR or PR versus those with SD at the different landmark time points.

LDH analyses based on the PD-L1 subgroup

We performed pretreatment analyses to account for the PD-L1 status as a known prognostic and predictive factor for patients undergoing ICI therapy. The PD-L1 status was defined as undetectable or low when PD-L1 expression was <1% on both tumor and tumor-infiltrating cells (TC0 or IC0), and the PD-L1 status was defined as positive when PD-L1 expression was 1% and <50% on tumor cells or ≥1% and <10% on tumor-infiltrating cells (TC1/2 or IC1/2) or ≥50% on tumor cells or ≥10% on tumor-infiltrating cells (TC3 or IC3).

Analyses were not adjusted for multiple testing; all *P* values were 2-sided.

RESULTS

Among the 1512 patients eligible for analysis (1225 in OAK and 287 in POPLAR), 132 had *EGFR* mutations, 8 had *EMLA-ALK* translocations, and 45 had missing pretreatment LDH values; this left 1327 (88%) for analysis (Supporting Fig. 1). The median follow-up was 18.9 months (range, 0.03-24.9 months).

Baseline characteristics are summarized in Supporting Table 1. The median pretreatment LDH level was 234 U/L (range, 185-347 U/L). Most patients were male, previous smokers with nonsquamous stage IV NSCLC and baseline LDH levels within the normal range.

Prognostic Value of Pretreatment LDH

Patients with elevated pretreatment LDH had a higher risk of progression (hazard ratio [HR], 1.33, 95% confidence interval [CI], 1.18-1.49; $P < .0001$) and death (HR, 1.40; 95% CI, 1.22-1.59; $P < .0001$) than those with LDH within the normal range (Supporting Table 1). Among patients treated with atezolizumab, the median PFS and OS were significantly shorter for elevated LDH versus normal-range LDH (PFS, 1.5 vs 3.2 months; HR, 1.35; 95% CI, 1.15-1.60; $P = .004$; OS, 9.5 vs 15.3 months; HR, 1.49; 95% CI, 1.23-1.81; $P = .0001$; Fig. 1A,C). Similar findings were observed among those treated with docetaxel. LDH remained a significant independent variable in multivariate analysis (HR for PFS, 1.30; 95% CI, 1.15-1.46; $P < .001$; HR for OS, 1.38; 95% CI, 1.20-1.58; $P < .001$; Supporting Table 2) with a similar magnitude of effect for both treatment arms (Supporting Tables 3 and 4).

Predictive Value of Pretreatment LDH

Among patients with LDH within the normal range, the median OS for atezolizumab and docetaxel was 15.3 and 10.7 months, respectively (HR, 0.70; 95% CI, 0.58-0.83; $P = .0001$). Among patients with elevated LDH, the median OS for those receiving atezolizumab and docetaxel was 9.5 and 8.6 months, respectively (HR, 0.84; 95% CI, 0.69-1.02; $P = .08$). Pretreatment LDH, whether normal or elevated, did not identify a differential benefit in favor of either atezolizumab or chemotherapy for OS (interaction $P = .28$; Fig. 2).

We found similar results for PFS. Among patients with LDH within the normal range, the median PFS for atezolizumab and docetaxel was 3.2 and 4.1 months, respectively (HR, 0.86; 95% CI, 0.74-1.01; $P = .06$). Among those with elevated LDH, the median PFS was 1.5 and 2.8 months, respectively (HR, 1.001; 95% CI, 0.84-1.20; $P = .99$). Therefore, the LDH level did not predict the additional benefit of either atezolizumab or chemotherapy (interaction $P = .42$; Fig. 2).

On-Treatment Value of LDH

Most patients had LDH within the normal range at week 6 (61%) and week 12 (66%), and only a minority experienced a change in LDH (Supporting Table 5).

Elevated LDH at week 6 among patients treated with atezolizumab was associated with worse PFS (HR, 1.36; 95% CI, 1.06-1.74; $P = .02$) and OS (HR, 1.54; 95% CI, 1.20-1.96; $P = .0008$). The risks of disease progression and death were similar as of the baseline and at the other time points of 12, 18, and 24 weeks (Figs. 3A and 4A). We found similar results among patients treated with docetaxel (Figs. 3B and 4B). Notably, patients who experienced a change in LDH from low to high or from high to low at week 6 experienced risks of progression and death similar to those of patients with LDH levels that remained high or remained low, respectively (Supporting Table 6).

A change in LDH at week 6 was not associated with a clinical benefit at 12 weeks after adjustments for the following: ECOG status; histology; PD-L1 status; presence of bone, liver, or bone metastases; and interaction with treatment (data not shown). At the 6-week landmark time point, among patients treated with either treatment, the median OS was shorter with elevated LDH versus normal-range LDH among patients with CR or PR (16.2 vs 23.2 months; HR, 2.10; 95% CI, 1.03-4.30; $P = .04$) as well as those with SD (12.6 vs 18.2 months; HR, 1.50; 95% CI, 1.22-1.85; $P < .001$), with adjustments made for other prognostic

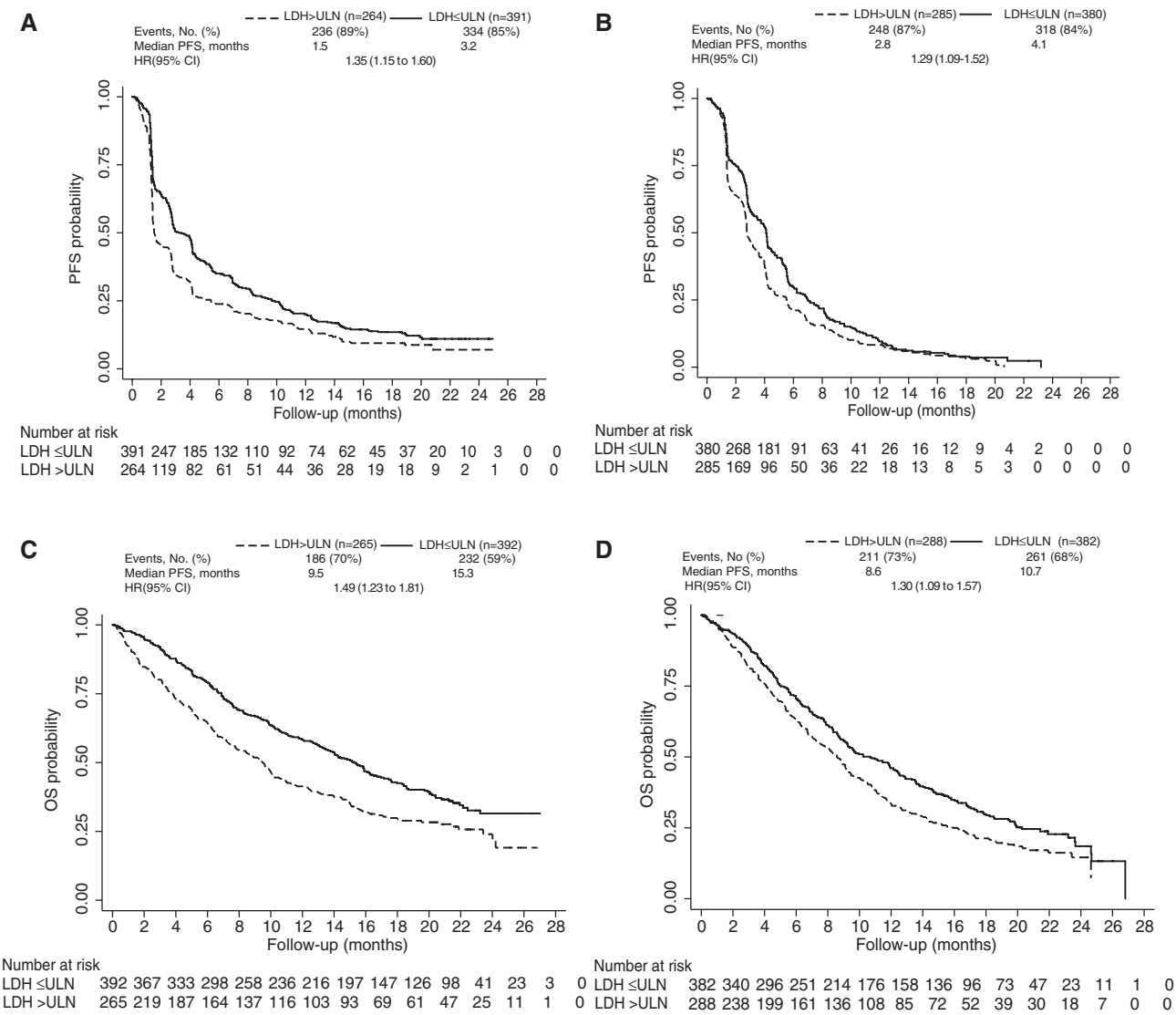

Figure 1. Pretreatment LDH (high vs normal) as a prognostic marker: (A,B) PFS in the atezolizumab and docetaxel arms, respectively, and (C,D) OS in the atezolizumab and docetaxel arms, respectively. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal (based on the local laboratory cut point).

factors. Similar PFS findings were observed for patients with CR or PR as well as those with SD (Fig. 5). Similar findings were also noted for the 12-week landmark time point (data not shown).

LDH Analyses by PD-L1 Status

When patients treated with atezolizumab were stratified by the PD-L1 status, elevated pretreatment LDH was associated with worse PFS (HR, 1.50; 95% CI, 1.15-1.94; $P = .003$) and OS (HR, 1.67; 95% CI, 1.24-2.26; $P = .0008$) among those with low or undetectable PD-L1 expression (TC0/IC0). Among those with TC1/2 or IC1/2, elevated pretreatment LDH was similarly associated with worse PFS but did not reach statistical significance (Fig. 6). We were unable to perform a correlative analysis for the TC3/IC3 subgroup because of the small numbers.

DISCUSSION

Our analysis of the POPLAR and OAK trials found no evidence for pretreatment LDH being able to predict a benefit with atezolizumab over docetaxel in patients with advanced NSCLC treated with second- or later-line atezolizumab. Despite the lack of predictive

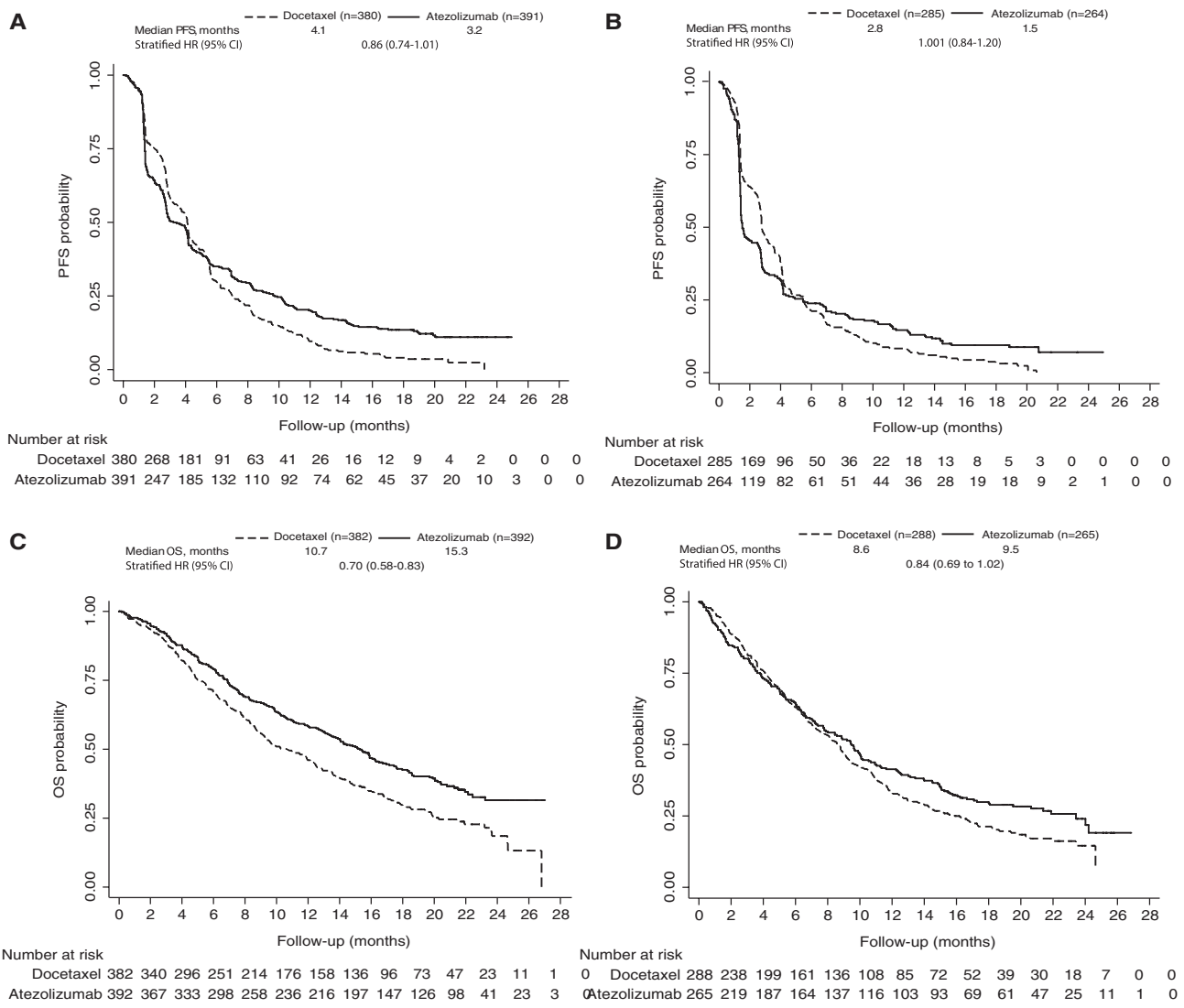

Figure 2. Pretreatment LDH as a predictive marker for atezolizumab benefit: (A,B) PFS by treatment arm in patients with LDH within the normal range and patients with elevated LDH, respectively, and (C,D) OS by treatment arm in patients with LDH within the normal range and patients with elevated LDH, respectively. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

ability, LDH is a robust and independent pre- and on-treatment prognostic marker even after we account for the PD-L1 status. As an on-treatment prognostic marker, LDH predicted the risk of progression and death at landmark time points similarly to that of the baseline. Furthermore, among patients experiencing an objective response or SD and receiving atezolizumab or docetaxel, on-treatment LDH can help to identify a poorer prognostic subgroup.

There is an unmet need to validate promising predictive biomarkers for ICI therapy with high-quality RCT data[16,17] to optimize treatment selection and minimize harm by identifying patients likely to respond or progress early. However, there is considerable confusion in the literature surrounding predictive biomarkers for ICI therapy, where the terms *predictive* and *prognostic* are used interchangeably.[14,18] When one is referring to the prediction of treatment benefit, the term *predictive factor* identifies a patient group that benefits more from one treatment than an alternative treatment, whereas a *prognostic factor* predicts for a better outcome regardless of the treatment received.[19] Before our study, the evidence supporting candidate predictive biomarkers, including LDH, in patients with advanced NSCLC treated with ICIs was limited by

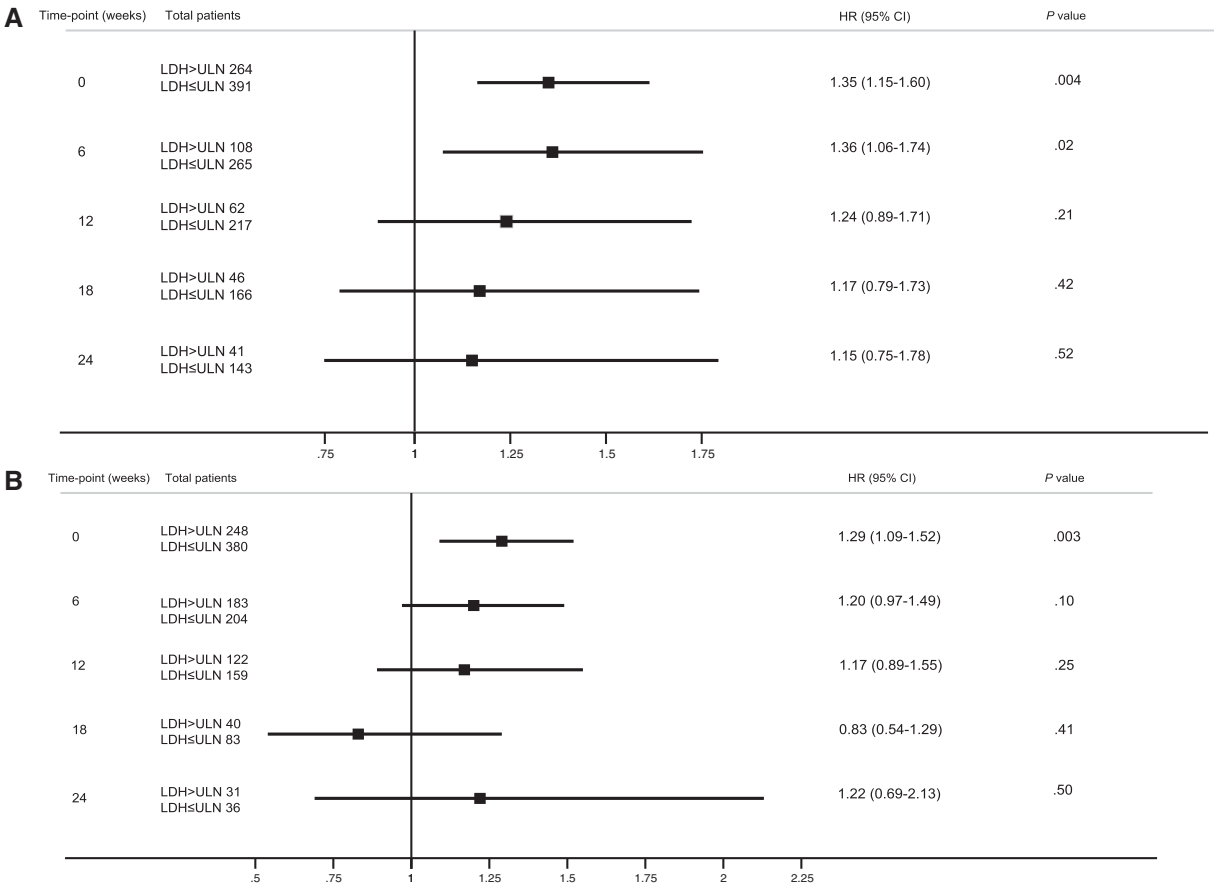

Figure 3. Landmark analysis of progression-free survival by LDH status at 0 to 24 weeks on treatment in (A) the atezolizumab arm and (B) the docetaxel arm. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal (based on the local laboratory cut point).

retrospective analyses, which cannot determine the independent causal effect of the biomarkers on therapeutic efficacy.[20,21] By using RCTs to compare 2 treatments and minimize bias, our analysis provides strong evidence that LDH is not predictive for a benefit with ICIs over chemotherapy and should not be used to select patients for ICI therapy. We hypothesize that LDH may nonspecifically reflect cell or tissue injury during treatment and does not exclusively capture the tumor microenvironment response to ICI therapy.

The clinical utility of LDH lies in its prognostic ability. Our findings are consistent with earlier studies of pretreatment LDH as a prognostic marker in patients with advanced NSCLC treated with ICIs.[13,14,22-24] In a meta-analysis of retrospective studies of patients with NSCLC treated with ICIs, high pretreatment LDH was significantly associated with poor PFS and OS.[14] Furthermore, Mezquita et al[13] developed and validated a pretreatment lung immune prognostic index where patients with elevated LDH levels and derived neutrophil to lymphocyte ratios had worse disease control rates and OS when treated with ICIs but not chemotherapy. Our study adds to the literature by providing novel, clinically relevant evidence on the value of on-treatment LDH, including at the time of assessing the treatment response, and on the value of pretreatment LDH as an addition to PD-L1 expression, which has not been previously addressed.[13,14,22,23]

Our study comprehensively assessed the prognostic value of LDH beyond the start of therapy. Only a minority of patients experienced a change in LDH with chemotherapy or ICI therapy, and this was unexpected. Patients with elevated LDH at any given time point during the first 6 months of therapy had lower survival probabilities than patients with LDH within the normal range. Notably, the risk of progression or death remained similar at the landmark time points in comparison with the baseline. For example, a patient with an elevated LDH level at the baseline or at 6 months, who had not

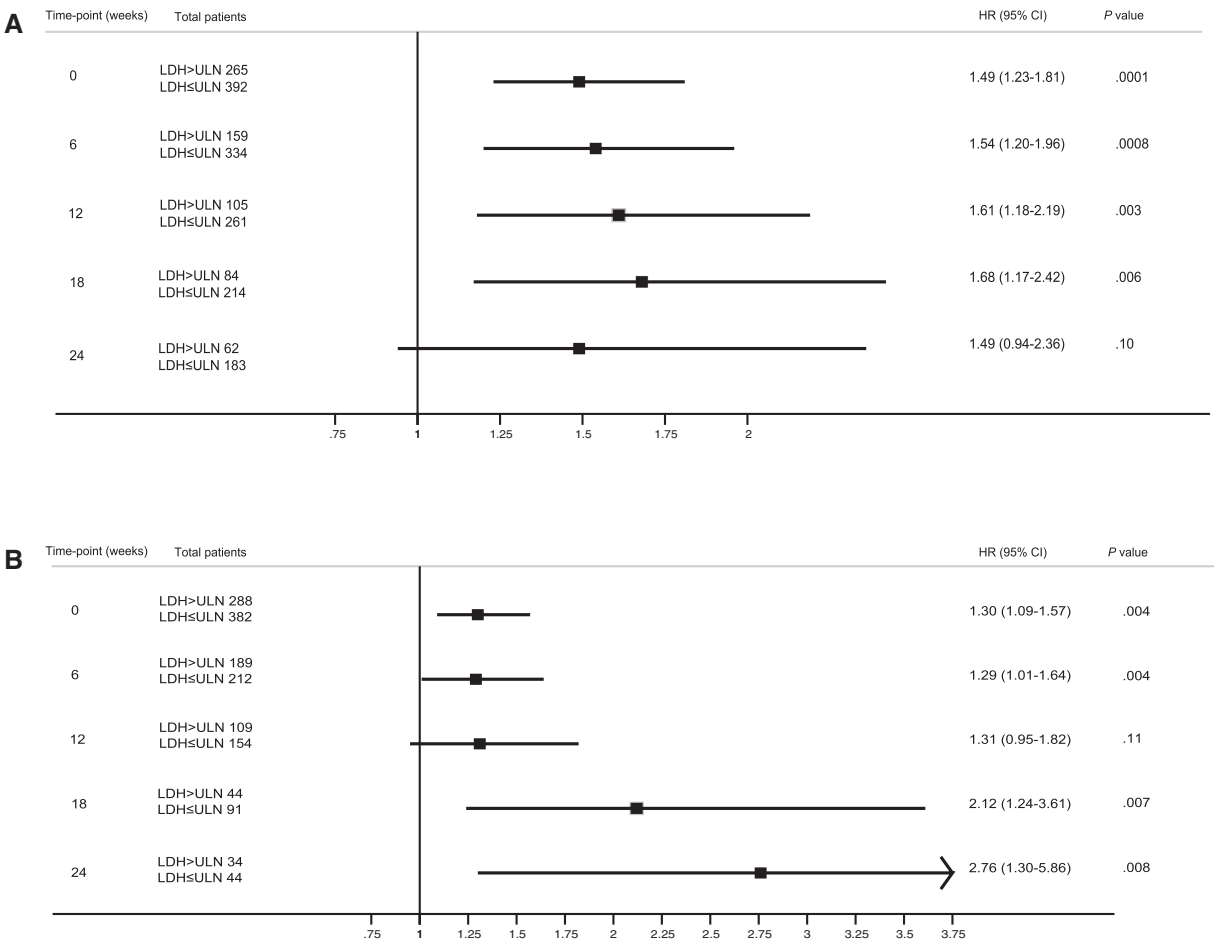

Figure 4. Landmark analysis of overall survival by LDH status at 0 to 24 weeks on treatment in (A) the atezolizumab arm and (B) the docetaxel arm. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal (based on the local laboratory cut point).

progressed earlier, had a 1.5-fold increase in the risk of death at both time points. Our findings support the robustness of LDH as a prognostic marker, both before and on treatment, that can inform patient and clinician discussions on prognosis beyond the baseline.

In both routine practice and trial settings, the radiologic response guides treatment decision-making. However, there is variability in individual survival outcomes regardless of radiologic response.[25] In a pooled analysis of 2 RCTs of chemotherapy versus nivolumab in patients with advanced NSCLC, among patients treated with nivolumab experiencing a radiologic response, only approximately 1 in 3 derived durable responses after 2 years.[25] Our findings demonstrate that among patients with either an objective response or SD, an elevated LDH status at the time of first computed tomography imaging identifies a poorer prognosis subgroup in comparison with patients with LDH within the normal range. However, further research is required, as we do not advocate using on-treatment LDH as a sole determinant for decisions around treatment cessation. Others have reported the potential value of combining the baseline and the relative change in LDH on treatment with C-reactive protein, the neutrophil to lymphocyte ratio, and the tumor size to develop a risk score to predict radiological disease progression.[24] In particular, future studies could focus on validating pre- and on-treatment LDH combined with other inflammatory and/or novel biomarkers such as circulating tumor DNA[26,27] as part of a risk tool using high-quality and large data sets. A reliable and robust risk tool would be helpful for distinguishing pseudo-progression from true radiological progression and for risk-stratifying patients and determining whether those of poor risk would benefit from escalation to combination therapy.

In comparison with prior studies,[9,13,14] we have demonstrated more robustly the prognostic value of

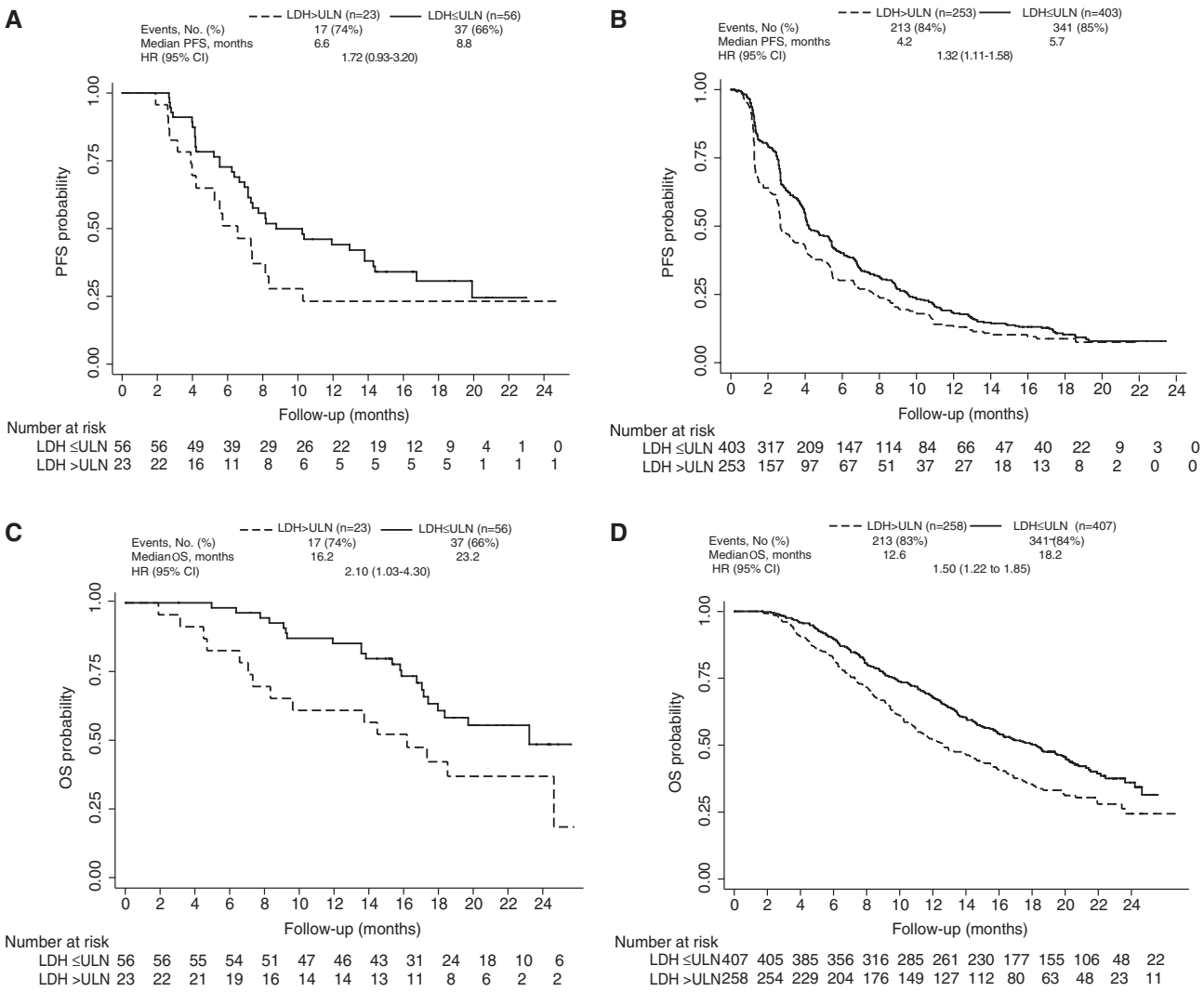

Figure 5. Landmark analysis stratified by the LDH status at 6 weeks: (A,B) PFS in patients with a partial/complete response and patients with stable disease, respectively, and (C,D) OS in patients with a partial/complete response and patients with stable disease, respectively. HRs were adjusted for the Eastern Cooperative Oncology Group status; histology; PD-L1 status; and presence of brain, liver and bone metastases. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; ULN, upper limit of normal (based on the local laboratory cut point).

pretreatment LDH by accounting for PD-L1 expression. An elevated pretreatment LDH level was significantly associated with worse outcomes among patients with low or undetectable PD-L1 expression (TC0/IC0) treated with atezolizumab or docetaxel. Among those with positive PD-L1 expression (TC1/2/3 or IC1/2/3) treated with atezolizumab, an elevated pretreatment LDH level was associated with a nonsignificant trend of worse PFS and OS; this likely reflected the small patient numbers. Further studies with larger sample sizes are needed to validate this finding.

A major strength of our study is our use of high-quality RCT data sets with more than 1300 participants and with pretreatment LDH values as well as the PD-L1 status available for almost all patients. In particular, these data sets of randomized comparisons between ICIs and chemotherapy provide unconfounded comparisons of these 2 classes of treatment. Our longitudinal analysis of on-treatment LDH adds to the limited data on the value of LDH as a prognostic marker beyond the baseline in patients with advanced NSCLC treated with ICIs and provides guidance on the clinical interpretation of LDH.

We acknowledge the limitations and weaknesses of our study. Although ICIs are now routinely used as first-line management of advanced NSCLC, our findings from RCTs of second and subsequent lines are still relevant and applicable. Our analysis is specifically based on

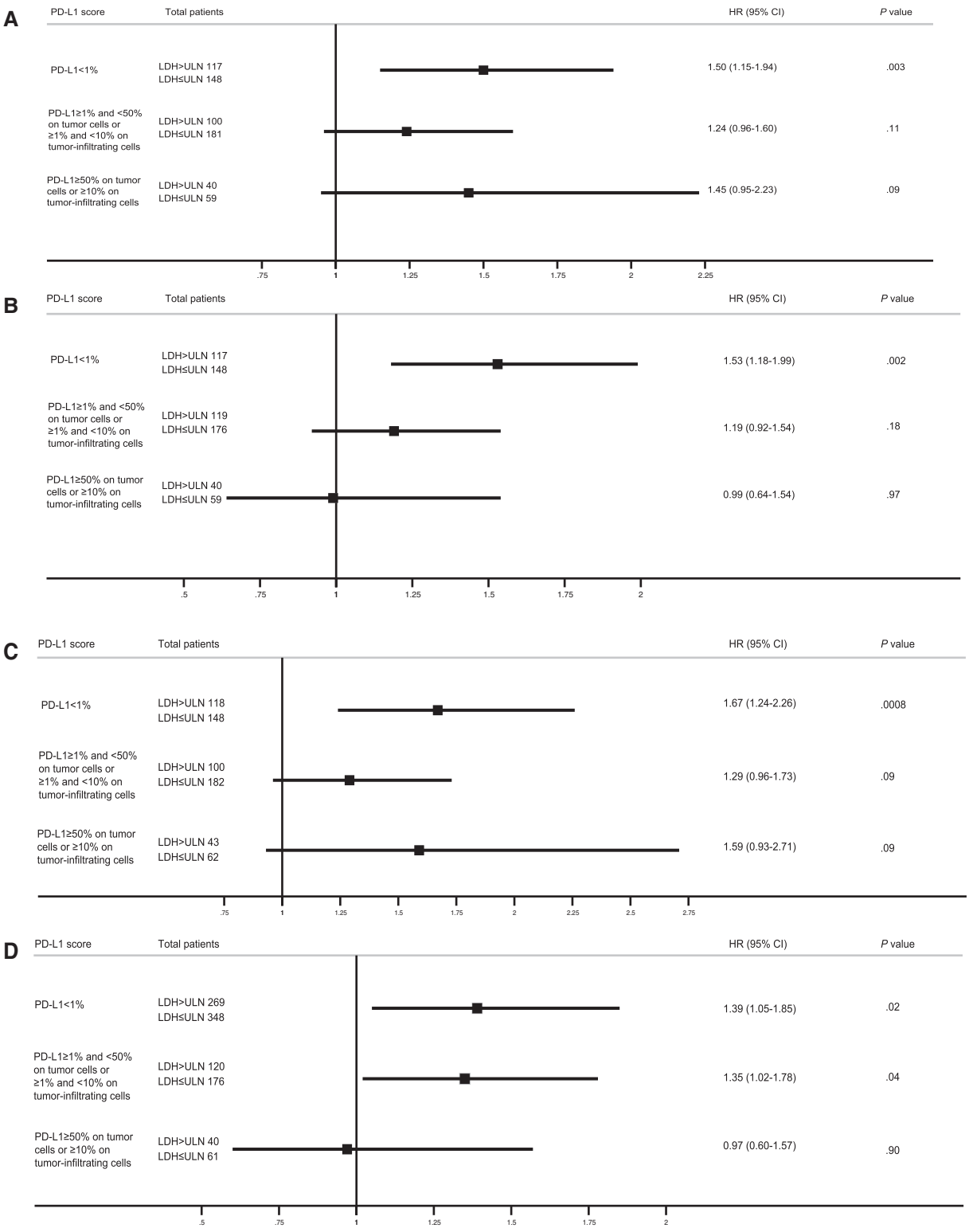

Figure 6. (A,B) Progression-free survival by baseline LDH (high vs normal) stratified by the PD-L1 status in the atezolizumab and docetaxel arms, respectively, and (C,D) OS by baseline LDH (high vs normal) stratified by the PD-L1 status in the atezolizumab and docetaxel arms, respectively. CI indicates confidence interval; HR, hazard ratio; LDH, lactate dehydrogenase; PD-L1, programmed death ligand 1; ULN, upper limit of normal.

2 large RCTs of atezolizumab, and the generalizability of these results needs to be confirmed for other ICI agents. Despite our pooled analysis, our analyses based on PD-L1 subgroups were limited by the sample size, and further larger studies are required. By using trial data sets, our study did not include patients with a poor performance status. However, our findings regarding the prognostic value of pretreatment LDH are consistent with retrospective studies of real-world patients.[9,13,14]

In conclusion, LDH is a useful pre- and on-treatment prognostic marker that can assist clinicians in counselling patients with advanced NSCLC undergoing second- or later-line atezolizumab or docetaxel. However, our findings fail to support the use of LDH as a predictive biomarker for ICI therapy. Future studies should rigorously validate promising predictive biomarkers with randomized data.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Angelina Tjokrowidjaja: Study concept, data acquisition and analysis, interpretation of the results, and writing and revision of the manuscript. **Sarah J. Lord:** Data interpretation, manuscript review, and supervision. **Thomas John:** Data interpretation, manuscript review, and supervision. **Craig R. Lewis:** Data interpretation, manuscript review, and supervision. **Peey-Sei Kok:** Methodology, data interpretation, and manuscript review. **Ian C. Marschner:** Data interpretation, manuscript review, and supervision. **Chee K. Lee:** Study concept, data acquisition, methodology, data interpretation, manuscript review, and supervision.

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