## Title

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# Elevated Hemoglobin A1c and the Risk of Developing ARDS in Two Cohort Studies

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## Abstract

**BACKGROUND:** Only a subset of patients at risk for ARDS go on to develop it, and the contribution of preexisting comorbidities (eg, diabetes) to ARDS risk is not well understood. Prior studies of the association between diabetes and ARDS have yielded conflicting results.

**RESEARCH QUESTION:** Does assessing ARDS risk based on hemoglobin A1c (HbA1c) as a marker of long-term blood glucose levels, rather than a charted diagnosis of diabetes, clarify the relationship between diabetes and ARDS?

**STUDY DESIGN AND METHODS:** Using data from two prospective observational cohorts of critically ill adults (Validating Acute Lung Injury Biomarkers for Diagnosis [VALID] and Early Assessment of Renal and Lung Injury [EARLI]), we analyzed the association between clinical HbA1c category and development of ARDS in patients with a risk factor for ARDS and at least one clinical HbA1c measurement within the 180 days prior through 14 days after enrollment.

**RESULTS:** A total of 599 patients in VALID and 276 in EARLI met inclusion criteria, of whom 164 and 58 developed ARDS, respectively. Patients with a charted diagnosis of diabetes were not shown to be more likely to develop ARDS (VALID: 24.6% ARDS in those categorized as nondiabetic vs 30.0% in those categorized as diabetic, $P = .14$; EARLI: 19.6% vs 22.8%, respectively; $P = .55$). However, in VALID, patients categorized as diabetic with inadequate glycemic control based on their HbA1c had an increased risk of developing ARDS compared with those with nondiabetic HbA1c (20.9% vs 34.0%, respectively; $P = .0073$), a finding that persisted in multivariable analysis (OR for those categorized as diabetic with inadequate glycemic control vs those categorized as nondiabetic range HbA1c, 1.25; 95% CI, 1.01–1.57). These findings were not reproduced in the smaller EARLI cohort, but were appreciated when the cohorts were combined for analysis.

**INTERPRETATION:** Elevated HbA1c may be associated with risk of developing ARDS, independent of clinical diagnosis of diabetes, but prospective validation is needed. If confirmed, these findings suggest that inadequate glycemic control could be an unrecognized risk factor for ARDS.

### Keywords

ARDS; chronic hyperglycemia; critical illness; diabetes; glycemic control

ARDS is a life-threatening cause of respiratory failure commonly observed in critically ill patients characterized by noncardiogenic pulmonary edema, severe hypoxemia, widespread alveolar-capillary barrier leakage, and reduced lung compliance.[1] ARDS can be triggered by a variety of precipitating events including direct lung injury from disorders such as pneumonia or aspiration of gastric contents, and indirect lung injury from conditions including sepsis, severe traumatic injuries, or pancreatitis.[1] However, not all patients with these insults go on to develop ARDS, and the factors that promote progression to ARDS remain unclear. Given the significant morbidity and mortality of ARDS, defining specific patient features that alter the risk of developing ARDS is an important area of exploration because this may support the development of targeted interventions.

A patient's individual risk of developing ARDS may vary by preexisting comorbidities. Prior studies have reported that a significant proportion of patients with ARDS have comorbid medical conditions and that comorbidities are associated with greater illness severity, organ dysfunction, and mortality.[2,3] However, studies of specific comorbidities, particularly diabetes mellitus, have yielded conflicting results. Diabetes is a common medical condition, affecting approximately 537 million adults worldwide[4] and 20% to 40% of critically ill patients.[5,6] Several studies found a decreased likelihood of ARDS in patients with a charted diagnosis of diabetes and at least one risk factor for ARDS.[7–9] Additionally, one meta-analysis of seven cohort studies reported that diabetes was independently associated with a reduced risk of ARDS.[10] In contrast, an analysis of a global multicenter, prospective observational cohort found no significant association between ARDS and diabetes, and others have reported similar results.[5,11]

These inconsistent findings suggest that the relationship between diabetes and the risk of ARDS may be more complex than previously appreciated. Diabetes is underdiagnosed, and there is considerable heterogeneity among patients regarding type of diabetes, medications used for treatment, and glycemic control.[6] These factors likely contribute to the variable findings in prior studies of the impact of diabetes on ARDS risk. We therefore investigated how the degree of chronic hyperglycemia, rather than a chart diagnosis of diabetes, affects ARDS risk. Hemoglobin A1c (HbA1c) provides an estimate of the average blood glucose level over the preceding 3 months and is the criterion standard for assessing glycemic control.[6] We hypothesized that chronic hyperglycemia as measured by HbA1c is associated with increased development of ARDS among at-risk critically ill adults.

## Study Design and Methods

### Study Population

We performed a subanalysis of two prospective observational cohort studies of critically ill adults: Validating Acute Lung Injury Biomarkers for Diagnosis (VALID) and Early Assessment of Renal and Lung Injury (EARLI). The inclusion and exclusion criteria for VALID and EARLI have been described previously.[12] Briefly, patients were enrolled in VALID from 2007 to 2020 and were admitted to one of four ICUs (medical, surgical, cardiovascular, or trauma) at an academic medical center in Nashville, Tennessee (Vanderbilt University Medical Center), and remained in the ICU for ≥ 2 days. Patients were enrolled in the EARLI cohort from 2008 to 2019 and were admitted from an ED to an ICU at a tertiary care academic medical center (UCSF Health) or an urban safety net hospital (Zuckerberg San Francisco General) in San Francisco, California. Details regarding informed consent have been previously described.[12] Both studies were approved by their respective institutional review boards (VALID No. 051065, EARLI No. 10–02852). This paper meets the guidelines for the Strengthening the Reporting of Observational Studies in Epidemiology statement.[13]

Patients were included in this study if they had a documented risk factor for ARDS[14] and at least one clinical HbA1c measurement within the 180 days prior through 14 days after enrollment. The 6-month time frame was selected because it is commonly used in studies of antidiabetic treatment patterns and medication adherence.[15,16] If patients had more than one

HbA1c measurement, the value closest to study enrollment was used for analysis. Clinical data such as demographics, medical history including a charted diagnosis of diabetes, medications, severity of illness scores (Acute Physiology and Chronic Health Evaluation II [APACHE II]), and lowest $Pa_{O_2}/F_{IO_2}$ ratio, and outcome data on use of mechanical ventilation, length of ICU stay, and hospital mortality were abstracted from the electronic medical record by trained research nurses. Patients were classified as having ARDS by two physician investigators' review of the participants' medical records to determine if they met the Berlin criteria for ARDS[14] on at least one of the first four ICU days in VALID and one of the first five ICU days in EARLI. LBW and JAB completed ARDS classification in VALID; CSC, MAM, AG, and CH contributed to ARDS classification for EARLI.

## Outcomes

The primary outcome of this study was development of ARDS. Secondary outcomes included illness severity metrics ($Pa_{O_2}/F_{IO_2}$ ratio and APACHE II score), duration of mechanical ventilation, length of ICU stay, and hospital mortality.

## Statistical Analysis

The study populations from each cohort were classified by clinical HbA1c categories as defined by the American Diabetes Association.[17] Patients with an HbA1c of ≤ 5.6% were classified as nondiabetic and those with an HbA1c of 5.7% to 6.4% were categorized as prediabetic. Patients in the HbA1c range of 6.5% to 6.9% were defined as diabetic with adequate glycemic control, whereas those with an HbA1c ≥ 7.0% were classified as diabetic with inadequate glycemic control.[17] Descriptive statistics were used to summarize baseline differences between cohorts and between HbA1c categories for each cohort, including frequencies with proportions for categorical variables and medians with interquartile ranges for continuous variables. Baseline characteristics and outcomes by HbA1c category were analyzed using the $\chi^2$ test for categorical variables and *t* test (or Mann-Whitney for nonparametric) or analysis of variance (or Kruskal-Wallis for nonparametric) for continuous variables. We used the $\chi^2$ test for trend (Cochran-Armitage test) to analyze differences in ARDS risk by HbA1c category, and the Jonckheere-Terpstra trend test for differences in APACHE II score or $PaO_2/FIO_2$ ratio by HbA1c category. To account for potential confounding variables, we applied multivariable logistic regression modeling to control for age, sex, race, smoking status, public vs private medical insurance source (public vs private as a proxy for socioeconomic status), charted diabetes diagnosis, use of antidiabetic medications (insulin, biguanides, or sulfonylureas), direct (eg, pneumonia) vs indirect (eg, sepsis) risk factors for ARDS, BMI, and APACHE II score. Additionally, to evaluate the possible presence of a nonlinear relationship between HbA1c and ARDS, we tested HbA1c as a continuous variable with a restricted cubic spline transformation and used the likelihood ratio test to assess the significance of the nonlinear component. The Shapiro-Wilk test was used to evaluate normality of data distribution. A two-sided *P* value < .05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism software version 9.5.0 for macOS. Because this was a convenience sample of all available patients in each cohort who met inclusion criteria and had a clinically measured HbA1c measurement, no prior sample size calculations were done.

# Results

## Baseline Characteristics

We studied 599 patients from VALID and 276 patients from EARLI who met inclusion criteria. The baseline characteristics for each cohort are summarized in e-Table 1. There were several significant differences between the patients in VALID and EARLI. Patients in VALID were younger and had higher severity of illness scores, BMIs, and rates of RBC transfusions (e-Table 1). HbA1c was measured prior to RBC transfusion for most (72.9% in VALID, 55.8% in EARLI) patients who required transfusion. Additionally, VALID had a slightly higher proportion of patients with a charted diagnosis of diabetes than those in EARLI (e-Table 1). VALID was also less racially diverse, had higher rates of tobacco use, and had a higher proportion of uninsured patients (11.7% vs 4.7%, respectively) than EARLI (e-Table 1). Tables 1 and 2 outline the baseline characteristics for each cohort's respective HbA1c categories. In VALID, patients with a higher HbA1c were older and a had higher BMI (Table 1). As expected, the presence of a clinical diagnosis of diabetes and use of antidiabetic medications increased across HbA1c categories (Table 1). There were also differences in ARDS risk factor between HbA1c categories, with more sepsis among patients with higher HbA1c. Notably, there was some discordance between HbA1c and charted diagnosis of diabetes in both cohorts, with a substantial proportion of patients with normal HbA1c levels (< 5.7%) having a clinical diabetes diagnosis (20.0% in VALID, 14.3% in EARLI) (e-Table 2) and a considerable proportion of patients with a diabetic range HbA1c (≥ 6.5%) not having any charted diabetes diagnosis (11.7% in VALID, 32.8% in EARLI) (e-Table 2).[4] Most charted diabetes diagnoses in both cohorts were for type 2 diabetes (e-Table 1). Most (68.1% in VALID, 57.4% in EARLI) clinical HbA1c measurements were obtained within 14 days of enrollment. Patients with higher HbA1c had HbA1c measured further from the time of enrollment in VALID, but not in EARLI (Table 1). Patients with higher HbA1c also had lower rates of private insurance coverage in both cohorts, but also slightly lower rates of current tobacco use (Table 1). Similar differences were seen between the HbA1c categories in EARLI (Table 2).

## Comparison of ARDS Risk by HbA1c Category in VALID

In VALID, 164 patients (27.4%) developed ARDS. A clinical diagnosis of diabetes was not associated with development of ARDS: 93 of the 310 patients with charted diabetes (30.0%) developed ARDS, whereas 71 of the 289 without charted diabetes (24.6%) developed ARDS ($P = .14$) (Fig 1A). However, when patients were stratified by clinical HbA1c classification, the likelihood of having ARDS significantly increased across the categories ($P = .0073$) (Fig 1B). In patients with nondiabetic range HbA1c, 48 (20.9%) developed ARDS, whereas 55 patients (34.0%) with inadequate glycemic control had ARDS, and this association persisted in a multivariable analysis controlling for potential confounders (OR for diabetic with inadequate glycemic control vs nondiabetic HbA1c, 2.13; 95% CI, 1.06–4.34) (e-Table 3). Among a subset of VALID patients for whom medication data were available (n = 589), use of insulin, biguanides, or sulfonylureas was not associated with a higher risk of ARDS (e-Table 4). The presence of a nonlinear relationship between HbA1c and ARDS was demonstrated when treating HbA1c as a continuous variable with a restricted cubic spline

transformation, as indicated by a significant likelihood ratio test for the nonlinear component (e-Table 5, Fig 1C).

### Comparison of Illness Severity and Clinical Outcomes by HbA1c Category in VALID

We next assessed illness severity based on HbA1c category by analyzing patients' APACHE II scores and lowest $Pa_{O_2}/F_{IO_2}$ ratios during the study period across categories of HbA1c among VALID patients. APACHE II scores significantly increased across the HbA1c categories ($P < .001$) (Fig 2A). The median APACHE II score for patients without diabetes was 24 (interquartile range [IQR], 19–29), whereas it was 28 (IQR, 23–34) for patients categorized as diabetic with inadequate glycemic control. Additionally, $Pa_{O_2}/F_{IO_2}$ ratios decreased by HbA1c category ($P = .022$) (Fig 2B), with a median lowest $Pa_{O_2}/F_{IO_2}$ ratio for patients with a nondiabetic range HbA1c of 182 (IQR, 129–241) compared with 153 (IQR, 107–220) for patients categorized as diabetic with inadequate glycemic control. We also analyzed differences in ventilator requirements, length of ICU stay, and mortality, none of which significantly differed between the categories of HbA1c. In patients with nondiabetic HbA1c, 172 patients (74.8%) required mechanical ventilation during their admission, and we observed similar rates across all other HbA1c categories ($P = .49$) (e-Fig 1A). The median ICU length of stay in the ICU and in-hospital mortality were also similar across the HbA1c categories (e-Figs 1B, 1C).

### Comparison of ARDS Risk, Illness Severity, and Clinical Outcomes by HbA1c Category in EARLI

We then sought to validate these findings in the 276 EARLI patients who met inclusion criteria, of whom 58 (21.0%) developed ARDS. There was no difference in risk of ARDS based on clinical diagnosis of diabetes; 28 of the 123 patients with charted diabetes (22.8%) developed ARDS, whereas 30 of the 153 patients without charted diabetes (19.6%) developed ARDS ($P = .55$) (Fig 3A). On stratification by HbA1c category, we observed numerically higher ARDS rates among patients in both the prediabetic (n = 17, 23.6%) and diabetes with inadequate glycemic control (n = 22, 24.4%) categories compared with those with nondiabetic HbA1c (n = 12, 17.1%), but this did not meet statistical significance ($P = .41$) (Fig 3B). A multivariable analysis controlling for the previously defined potential confounders, excluding use of antidiabetic medication because these data were not available in EARLI, also did not find an association between HbA1c category and ARDS (OR for diabetic with inadequate glycemic control vs nondiabetic HbA1c, 1.64; 95% CI, 0.54–5.20) (e-Table 6). We also did not observe any differences in APACHE II scores, lowest $Pa_{O_2}/F_{IO_2}$ ratios, ventilator use, or ICU length of stay across HbA1c categories in EARLI, but in-hospital mortality was significantly greater among patients with higher HbA1c (e-Fig 2, Fig 4). We also used restricted cubic splines to model the nonlinear relationship between HbA1c and ARDS in EARLI (Fig 3C); however, we did not identify a significant difference compared with a strictly linear model (e-Table 7).

## Analysis of ARDS Risk, Illness Severity, and Clinical Outcomes by HbA1c Category in Combined Cohorts

Due to the small sample size in EARLI, we also tested the association between HbA1c category and ARDS by combining the data from both cohorts. Similar to our previous analyses, a clinical diagnosis of diabetes was not associated with ARDS ($P = .09$), with 22.9% of patients categorized as nondiabetic and 27.9% of patients categorized as diabetic developing ARDS (e-Fig 3A). When patients were stratified by HbA1c categories, there was a significant association with ARDS risk in both the unadjusted ($P = .013$) (e-Fig 3B) and multivariable analyses (OR for diabetic with inadequate glycemic control vs nondiabetic HbA1c, 1.69; 95% CI, 1.05–2.74) (e-Table 8). A restricted cubic spline transformation was also applied to HbA1c as a continuous variable for the combined cohort data to investigate whether a nonlinear relationship between HbA1c and ARDS was present, but there was no significant difference from the linear model (e-Table 9). However, APACHE II scores did increase ($P < .001$) and lowest $Pa_{O_2}/F_{IO_2}$ ratios decreased across the categories ($P = .03$) (e-Figs 3D, 3E). There were no differences in ventilator use, length of ICU admission, or mortality by HbA1c category (e-Fig 4).

## Discussion

In this study, we report that critically ill patients at risk for ARDS with inadequate glycemic control, as evidenced by higher HbA1c, were significantly more likely to develop ARDS among patients at risk in the VALID cohort in both univariate and multivariate analyses. In contrast, a clinical diagnosis of diabetes was not associated with development of ARDS. Additionally, we found that illness severity, as determined by APACHE II score and lowest $Pa_{O_2}/F_{IO_2}$ ratio, worsened as HbA1c increased. Furthermore, we demonstrate that there is a nonlinear relationship between HbA1c and ARDS in VALID. These findings were not recapitulated in a smaller independent cohort (EARLI), leading to some residual uncertainty about the relationship between HbA1c and ARDS. However, there are several differences, including demographic and clinical features, between VALID and EARLI that could explain these results. Specifically, the EARLI cohort is smaller, and the patients in VALID were less racially diverse, had higher BMIs and APACHE II scores, and had greater rates of tobacco use. When the cohort data were combined, higher HbA1c was once again significantly associated with higher rates of ARDS and greater illness severity, supporting low power and demographic differences as potential explanations for the different results between the two cohorts. Overall, these findings provide new insight into the complex interplay between diabetes and ARDS and highlight the importance of future investigations into the relationship between these pathologies.

Previous studies investigating the association between diabetes and the risk of developing ARDS have yielded conflicting results, with some showing a protective effect of diabetes and others showing no impact. One potential explanation for these conflicting data is how the presence of diabetes was defined in the study population. Prior studies have focused on a clinical history of diabetes,[5,7,8,10,11] which may have led to misclassification of study patients because diagnosis of diabetes is not uniform across patients. In our current study,

there was a considerable number of patients whose HbA1c fell into the diabetic (≥ 6.5%) range,[4] but who did not carry a charted diagnosis of diabetes. Potential explanations for this observation include differences in access to health care, rates of diabetes screening, documentation practices across institutions, or health care fragmentation. Conversely, a substantial proportion of our study population had normal HbA1c values (< 5.7%) but carried a clinical diagnosis of diabetes, which could be explained by adequate management of diabetes through strategies such as lifestyle modifications with dietary changes and weight loss, or the use of antidiabetic medications. The discordance between HbA1c and clinical diagnosis of diabetes indicates that relying on a chart diagnosis of diabetes may be insufficient for investigating associations between diabetes and ARDS. Thus, we sought to provide clarification about the relationship between diabetes and ARDS by using HbA1c to quantify chronic hyperglycemia.

Another potential explanation for the conflicting data in prior studies of diabetes and risk of ARDS is that it is chronic hyperglycemia and not a diagnosis of diabetes per se that confers increased risk. Hyperglycemia alone has been shown to increase inflammatory cytokine production, oxidative stress, and formation of advanced glycation end products.[18,19] AGEs promote endothelial dysfunction, and the receptor for advanced glycation end products is an established marker of acute lung injury.[20] In one study, the receptor for advanced glycation end products was measured in the plasma of patients from a randomized controlled trial of low tidal volume in acute lung injury.[20] Higher levels of the receptor for advanced glycation end products were associated with more severe lung injury, fewer ventilator-free and organ failure-free days, and increased mortality in the higher tidal volume group.[20] The effects of chronic hyperglycemia, particularly the generation of advanced glycation end products, represent a possible mechanism whereby higher HbA1c may reflect an altered inflammatory milieu that modifies the risk of developing ARDS. Future mechanistic studies are needed to test the effects of chronic hyperglycemia on biologic pathways related to the pathophysiology of ARDS.

Antidiabetic medications are additional plausible factors that might modulate the relationship between diabetes and risk of ARDS. Several therapies used in the management of diabetes are known to have immunomodulatory effects. Insulin, for example, decreases alveolar macrophage activation, proinflammatory cytokine production, and leukocyte adhesion and chemotaxis,[21,22] effects that could theoretically dampen the pathophysiologic processes that contribute to ARDS. Metformin also has antiinflammatory properties and has been shown to preserve alveolar-capillary barrier permeability in animal models of acute lung injury.[23,24] Additionally, liraglutide, a glucagon-like peptide-1 receptor agonist, was recently demonstrated to improve outcomes in a murine model of sepsis-induced acute lung injury.[25] These drug effects may point toward mechanisms by which lowering HbA1c with antidiabetic medications may influence ARDS pathogenesis. Although we did not detect a relationship between antidiabetic medication use (insulin, biguanides, or sulfonylureas) and ARDS in this analysis, future studies should specifically address the impact of antidiabetic therapies on ARDS risk.

Our study has several strengths. First, we used data from two large, prospective cohorts with demographically and clinically diverse patient populations. Additionally, the patients

are well phenotyped for ARDS and have a variety of ARDS risk factors, enhancing the generalizability of our findings. However, there are also some limitations. HbA1c measurements used in our analyses were restricted to those sent for clinical reasons, which limits power and introduces sampling bias. There was also a lag between HbA1c evaluation and study entry for some patients; however, most measurements were temporally close to enrollment. Future work using alternative measures of glycemic control (eg, fructosamine, glycated albumin) could minimize the concerns of bias and timing regarding HbA1c because these markers of chronic hyperglycemia can be measured in stored patient serum.[26] Additionally, fructosamine and glycated albumin are not influenced by physiologic RBC turnover or the receipt of blood transfusions, which are other factors that were not addressed by our investigation.[26] However, given that only about 10% of each cohort had an RBC transfusion that could have conceivably affected HbA1c level (ie, HbA1c measured after RBC transfusion), it is unlikely that RBC transfusions impacted our findings. Furthermore, HbA1c alone does not adequately encompass the full complexity of an individual's risk for ARDS because organ injury, metabolic abnormalities, and immunologic dysfunction secondary to chronic hyperglycemia are not captured in a single measurement. To better understand the effects of inadequate glycemic control over an extended duration, a longitudinal electronic health record study could be performed and thus represents an intriguing future direction for this work. Finally, information on prehospital antidiabetic medication use was only available in one cohort and may be limited by difficulties in ascertaining home medications at the time of enrollment, which could limit interpretation of our medication data. Future analyses should specifically examine the potential role of antidiabetic medications on ARDS development, severity, and outcomes.

## Interpretation

Prior studies of the association between diabetes and ARDS may have been hindered by underdiagnosis of diabetes and variability within the diabetic population regarding type of diabetes, medication regimens, and degree of glycemic control. Here, we report that, in one retrospective cohort, there was a significant association between higher HbA1c and risk of developing ARDS that was independent of a clinical diagnosis of diabetes. However, these findings were not consistent in a second, smaller independent cohort. These inconsistent results emphasize that the relationship between chronic hyperglycemia and risk of ARDS remains complex and unclear, likely in part due to the heterogeneity of both clinical entities. Overall, our findings suggest that inadequate glycemic control could be an unrecognized risk factor for ARDS that merits additional study, and prospective studies are needed to further investigate this relationship.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS:

| | |
|---|---|
| **APACHE II** | Acute Physiology and Chronic Health Evaluation II |
| **EARLI** | Early Assessment of Renal and Lung Injury |
| **HbA1c** | hemoglobin A1c |
| **IQR** | interquartile range |
| **VALID** | Validating Acute Lung Injury Biomarkers for Diagnosis |

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## Take-home Points

**Study Question:**

Does assessing ARDS risk based on hemoglobin A1c as a marker of glycemic control, rather than a charted diagnosis of diabetes, clarify the relationship between diabetes and ARDS?

**Results:**

In this analysis of two prospective observational cohort studies, we found no association between a clinical diagnosis of diabetes and the rate of ARDS development, but when patients were stratified by glycemic control, there was a significant association between higher hemoglobin A1c and likelihood of developing ARDS in one cohort; however, this was not seen in the second cohort.

**Interpretation:**

Chronic hyperglycemia may be an unrecognized risk factor for developing ARDS.

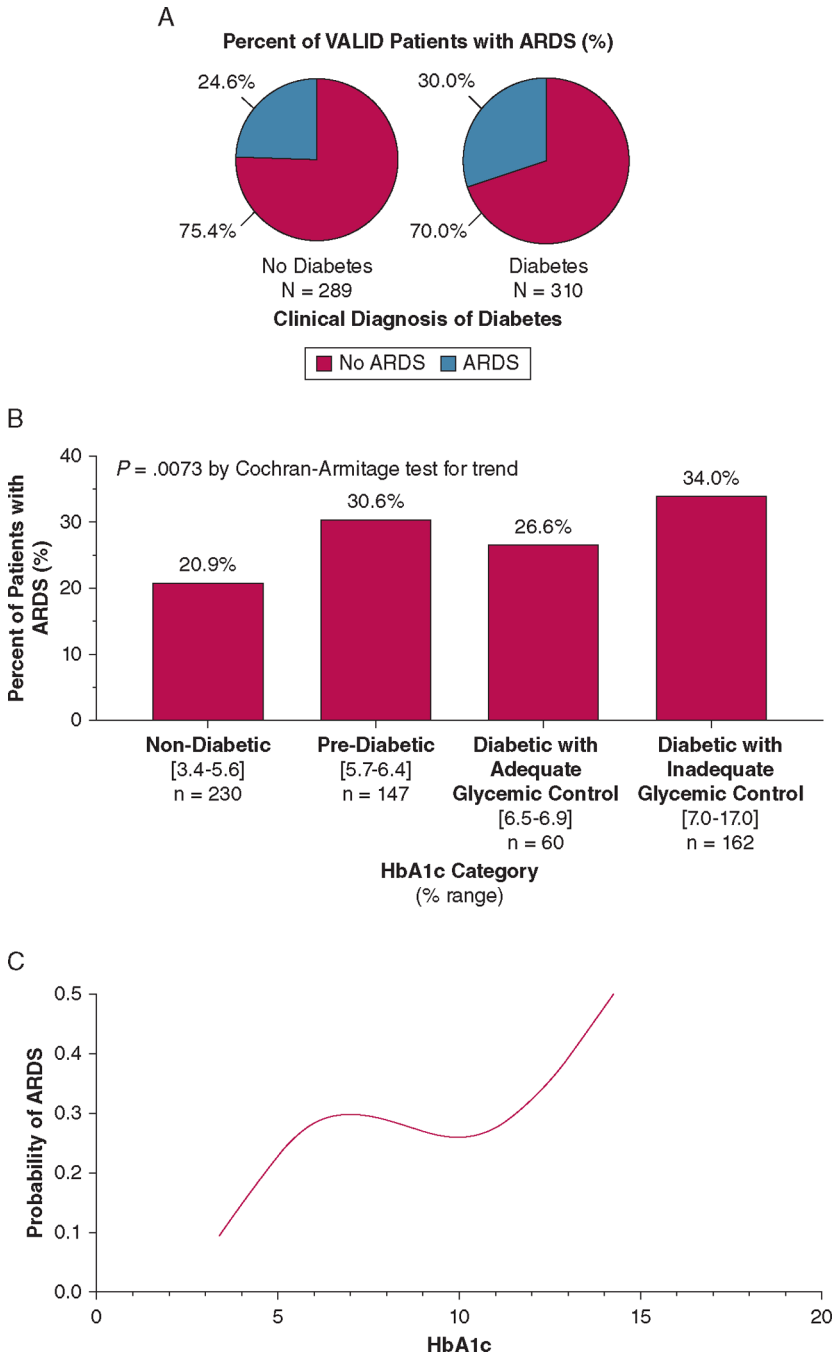


**Figure 1 –.**

A, Association between clinical diagnosis of diabetes and (B) HbA1c category and development of ARDS in VALID. C, Restricted cubic spline for probability of ARDS by HbA1c. HbA1c= hemoglobin A1c; VALID Validating = Acute Lung Injury Biomarkers for Diagnosis.

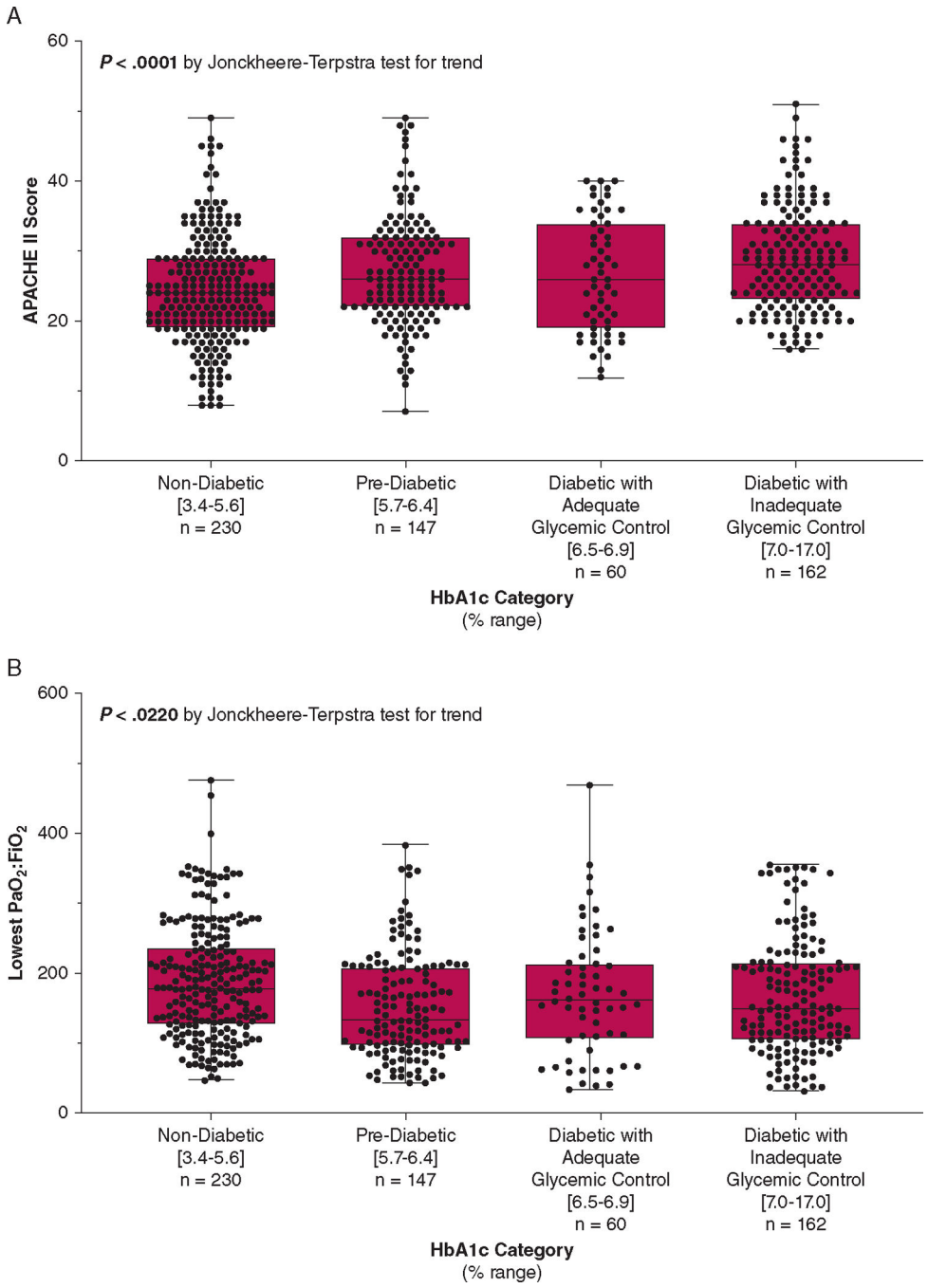


**Figure 2 –.**

A, B, Association between HbA1c category and (A) APACHE II score and (B) lowest $PaO_2/FIO_2$ ratios during the first 4 study days in Validating Acute Lung Injury Biomarkers for Diagnosis (VALID). APACHE II = Acute Physiology and Chronic Health Evaluation II; HbA1c = hemoglobin A1c.

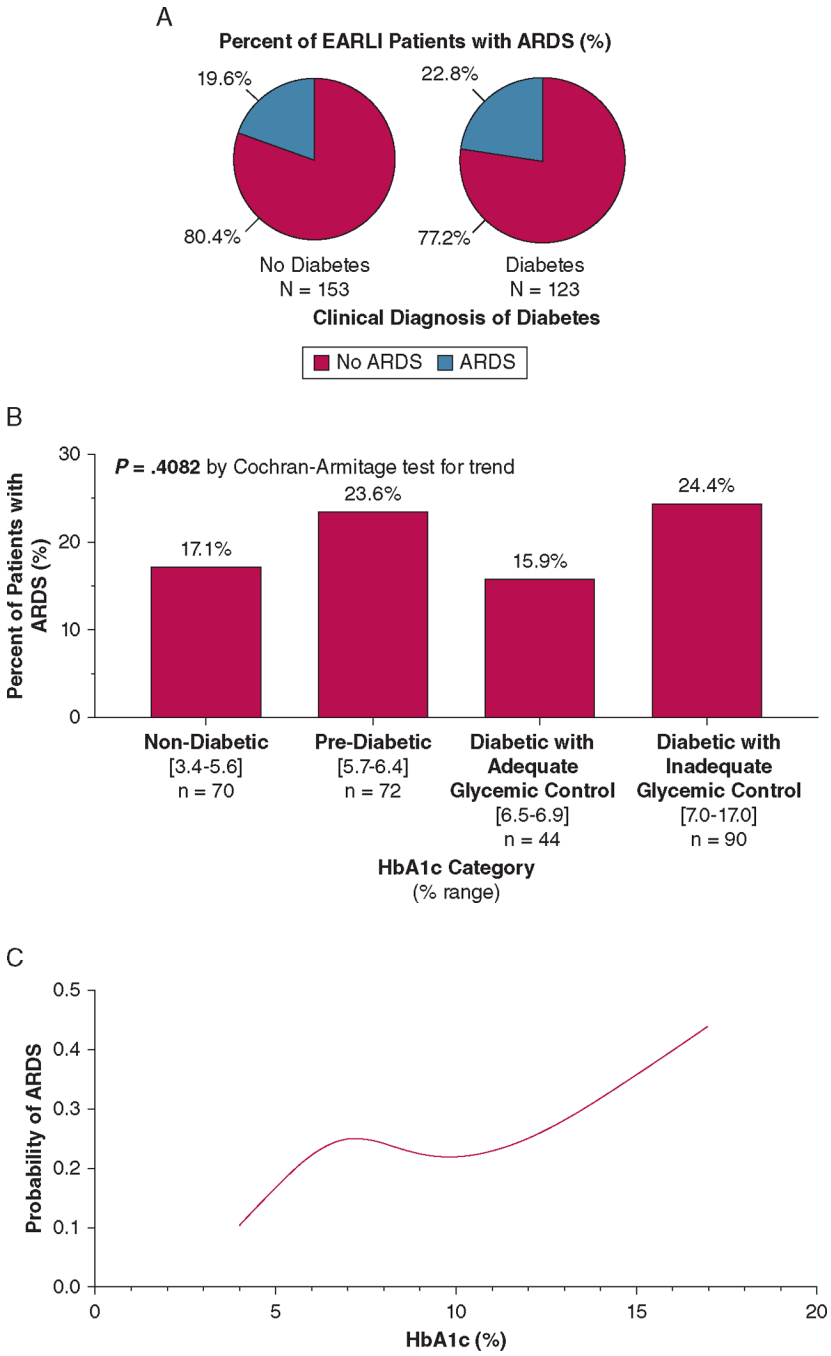


**Figure 3 –.**

A, Association between clinical diagnosis of diabetes and (B) HbA1c category and development of ARDS in EARLI. C, Restricted cubic spline for probability of ARDS by HbA1c. EARLI = Early Assessment of Renal and Lung Injury; HbA1c = hemoglobin A1c.

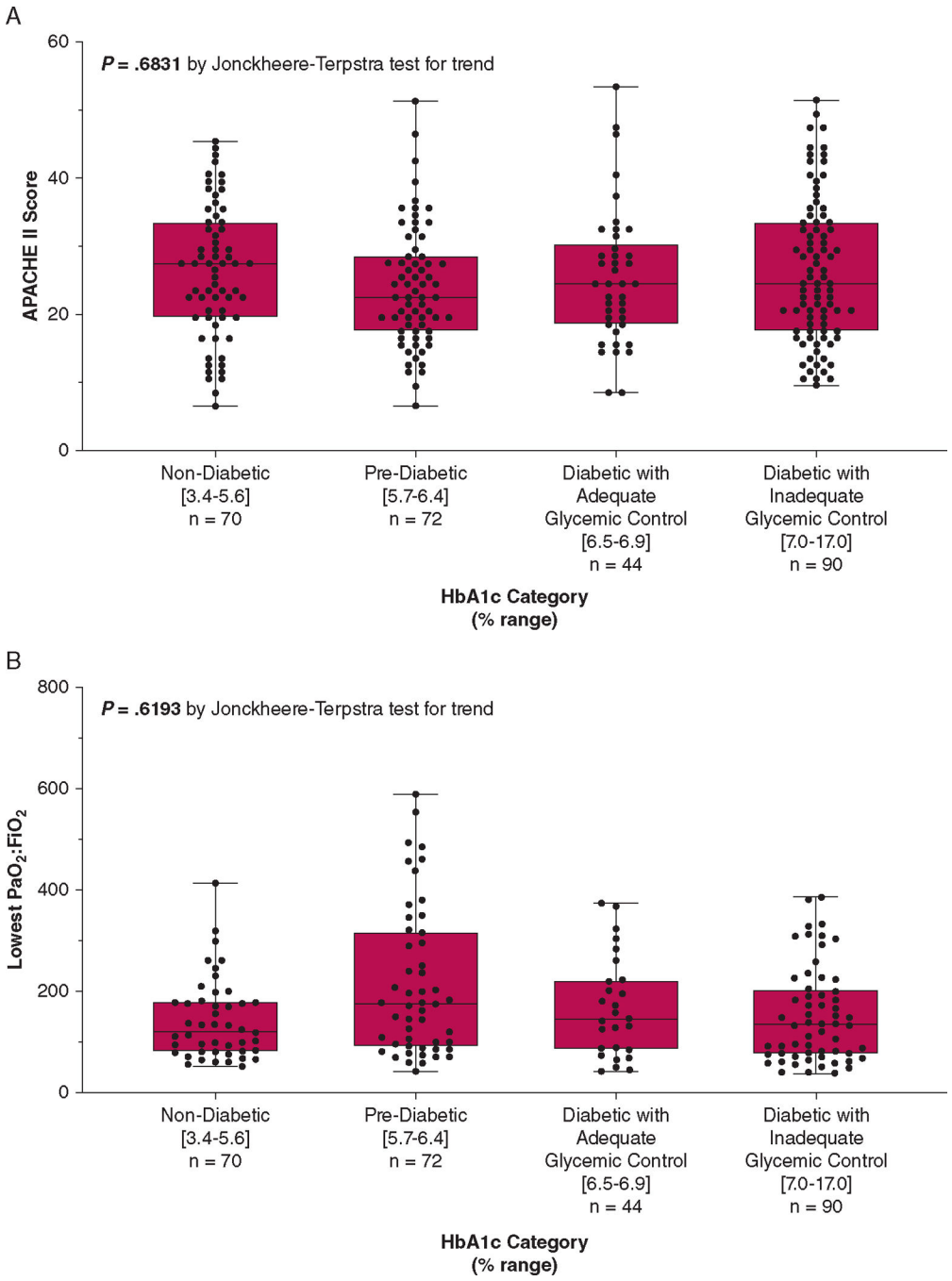


**Figure 4 –.**

A, Association between HbA1c category and APACHE II scores and (B) lowest $Pao_2/Fio_2$ ratios in EARLI. APACHE II = Acute Physiology and Chronic Health Evaluation II; EARLI = Early Assessment of Renal and Lung Injury; HbA1c = hemoglobin A1c.

**TABLE 1 ]**

Comparison of Demographics and Clinical Data by HbA1c Classification in Validating Acute Lung Injury Biomarkers for Diagnosis (VALID)

| Clinical HbA1c Category | Nondiabetic (n = 230) | Prediabetic (n = 147) | Diabetic With Adequate Glycemic Control (n = 60) | Diabetic With Inadequate Glycemic Control (n = l62) | *P* Value |
|---|---|---|---|---|---|
| HbA1c, %, range | 3.4 to 5.6 | 5.7 to 6.4 | 6.5 to 6.9 | 7.0 to 17.0 | ... |
| Time from enrollment to HbA1c measurement, d | −0.3 (−11.5 to 0.3) | −1.0 (−38.7 to 0.3) | −8.8 (−62.8 to −0.2) | −4.2 (−37.8 to 0.0) | .0004 |
| Age, y | 54 (45 to 63) | 59 (49 to 68) | 65 (52 to 70) | 59 (51 to 66) | < .0001 |
| Sex, female | 86 (37.4) | 59 (40.1) | 24 (40.0) | 70 (43.2) | .718 |
| Race, White | 197 (85.7) | 119 (81.0) | 51 (85.0) | 134 (82.7) | .974 |
| Currently smokes | 79 (34.3) | 59 (40.1) | 15 (25.0) | 44 (27.2) | .051 |
| Insurance status, private | 73 (31.7) | 32 (21.8) | 10 (16.7) | 44 (27.2) | .174 |
| Charted diagnosis of diabetes | 46 (20.0) | 68 (46.2) | 45 (75.0) | 151 (93.2) | < .0001 |
| Type of diabetes, type 2 | 45 (97.8) | 68 (98.6) | 40 (88.9) | 129 (85.4) | .0023 |
| BMI, $kg/m^2$ | 27 (24 to 33) | 29 (26 to 36) | 32 (23 to 37) | 31 (26 to 37) | .0035 |
| ARDS risk factor, sepsis | 74 (32.2) | 53 (36.1) | 29 (47.5) | 64 (40.1) | < .0001 |
| Use of antidiabetic medication | 23 (10.0) | 35 (23.8) | 21 (35.0) | 58 (35.8) | < .0001 |

Values are No. (%), median (interquartile range), or as otherwise indicated. HbA1c = hemoglobin A1c.

**TABLE 2 ]**

Comparison of Demographics and Clinical Data by HbA1c Classification in Early Assessment of Renal and Lung Injury (EARLI)

| Clinical HbA1c Category | Nondiabetic (n = 70) | Prediabetic (n = 72) | Diabetic With Adequate Glycemic Control (n = 44) | Diabetic With Inadequate Glycemic Control (n = 90) | *P* Value |
|---|---|---|---|---|---|
| HbA1c, %, range | 3.4 to 5.6 | 5.7 to 6.4 | 6.5 to 6.9 | 7.0 to 17.2 | ... |
| Time from enrollment to HbA1c measurement, d | 0.5 (−59.5 to 1.0) | 0.0 (−54.8 to 2.0) | −45.0 (−85.3 to 1.0) | 0.0 (−42.0 to 2.0) | .161 |
| Age, y | 62 (50 to 70) | 66 (56 to 78) | 69 (54 to 78) | 62 (47 to 72) | .030 |
| Sex, female | 26 (37.1) | 29 (40.3) | 19 (43.2) | 29 (32.2) | .588 |
| Race, White | 34 (48.6) | 25 (34.7) | 16 (36.4) | 31 (34.4) | .030 |
| Currently smokes | 8 (11.4) | 16 (22.2) | 4 (9.1) | 9 (10.0) | .114 |
| Insurance status, private | 16 (22.9) | 30 (41.7) | 9 (20.5) | 18 (20.0) | .021 |
| Charted diagnosis of diabetes | 10 (14.2) | 23 (31.9) | 27 (61.4) | 63 (70.0) | < .0001 |
| Type of diabetes, type 2 | 10 (100) | 23 (100) | 25 (92.6) | 51 (81.0) | .045 |
| BMI, $kg/m^2$ | 26 (22 to 31) | 27 (21 to 32) | 28 (24 to 35) | 28 (25 to 35) | .073 |
| ARDS risk factor, sepsis | 33 (47.1) | 30 (41.7) | 20 (45.5) | 45 (50.0) | .946 |

Values are No. (%), median (interquartile range), or as otherwise indicated. HbA1c = hemoglobin A1c.