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# Glucagon-Like Peptide-1 Is Prognostic of Mortality in Acute Respiratory Failure

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**OBJECTIVES:** The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) have therapeutic effects in diabetes mellitus. Prior clinical studies suggest incretins are prognostic of adverse outcomes in critical illness. We investigated whether incretin levels indicate disease severity and clinical outcomes in patients with acute respiratory failure, a common cause of critical illness.

**DESIGN:** Retrospective cohort study.

**SETTING:** ICUs in UPMC Health Systems hospitals within Western Pennsylvania.

**PATIENTS:** Two hundred ninety-seven critically ill adults with acute respiratory failure.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** We measured GLP-1 and GIP levels in baseline samples collected at the time of study enrollment. We compared incretin levels across subgroups differing by severity of illness and investigated associations between incretins and markers of systemic host responses and intestinal permeability. In our primary analysis, we tested the association of each incretin level with 90-day mortality by logistic regression in unadjusted analyses and in analyses adjusted for age, Sequential Organ Failure Assessment score, and circulating interleukin-6 levels. GLP-1 levels were higher in nonsurvivors and patients with or at-risk for acute respiratory distress syndrome compared to those intubated for airway protection. GLP-1 levels also positively correlated with systemic immune response biomarkers but not with markers of intestinal permeability. GLP-1 levels positively correlated with mortality in unadjusted (odds ratio, 1.99 [1.55–2.56]; $p < 0.01$) and adjusted (2.02 [1.23–3.31]; $p < 0.01$) analyses. GIP levels were not associated with mortality or with host response biomarkers.

**CONCLUSIONS:** GLP-1 but not GIP levels were positively associated with systemic inflammation and mortality in critically ill patients with acute respiratory failure. Increased circulating GLP-1 levels may serve as prognostic biomarkers to identify patients who are likely to have worse outcomes.

**KEYWORDS:** acute respiratory failure; critical illness; glucagon-like peptide-1; glucose-dependent insulinotropic peptide; incretin; inflammation; mortality

Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are intestine-derived peptides secreted from enteroendocrine cells in response to gut nutrient delivery. Under physiologic conditions, GLP-1 (released from the distal small bowel and colon) and GIP (released from the proximal small bowel) promote glucose-dependent release of insulin from pancreatic β cells to promote euglycemia, with pleotropic effects including induction of β-cell proliferation, suppression of glucagon release, increases in satiety, and anti-inflammatory effects in numerous cells and tissues. The therapeutic effects of incretins have led to the advent of popular incretin-based

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## KEY POINTS

**Question:** Do incretin hormone levels indicate adverse clinical outcomes in critically ill patients with acute respiratory failure?

**Findings:** In a secondary analysis of 297 patients with acute respiratory failure, higher glucagon-like peptide-1 (GLP-1) levels at the time of study enrollment were positively associated with systemic inflammatory responses and 90-day mortality.

**Meaning:** Higher circulating levels of GLP-1 are associated with adverse outcomes and increased severity of illness in acute respiratory failure. Associations with adverse outcomes were unique to GLP-1 and were not seen with the other major incretin, glucose-dependent insulinotropic peptide (GIP).

medications for diabetes and obesity, and the effectiveness of these medications has led to investigations into their use in other diseases (1).

Critical illness may result from a variety of insults such as sepsis or trauma but is characterized by multiple organ dysfunction resulting from aberrant and often uncontrolled immune responses. The gastrointestinal tract is hypothesized to have an important role in the mediation of systemic inflammation in critical illness (2). Intestinal barrier disruption in critical illness is associated with activation of inflammatory cascades, disturbed nutritional absorption, altered metabolic homeostasis, and translocation of pathogenic microbes or deleterious microbial products to systemic circulation, contributing to multiple organ injuries (3).

Prior studies have demonstrated that circulating GLP-1 concentrations increase in response to acute inflammation (4–6), and higher circulating GLP-1 levels are associated with adverse outcomes including increased mortality in patients with sepsis (7, 8), renal failure, and cardiogenic shock (7–10). However, limited knowledge exists characterizing how incretin levels are associated with systemic inflammation and mortality in acute respiratory failure (ARF), a common manifestation of critical illness.

## METHODS

### Overview

The goal of this study was to investigate circulating levels of incretin hormones as prognostic biomarkers of mortality in ARF. This population is broader and less targeted than some prior studies, but is reflective of patients admitted to ICUs for whom intestinal pathways are dysregulated and contribute to disease pathogenesis (11, 12). In our primary analysis, we tested each incretin hormone as a predictor of 90-day mortality by logistic regression in unadjusted and adjusted analyses. We performed several targeted secondary analyses to investigate underlying contributors to the associations between incretins and mortality, including systemic inflammation and increased intestinal permeability.

### Study Population

We performed a retrospective analysis of a cohort of adult patients with ARF enrolled in the Acute Lung Injury Registry and Biospecimen Repository (ALIR) at the University of Pittsburgh. Further details of the ALIR study have been previously published (13, 14). Briefly, ALIR enrolls patients 18–90 years old with ARF requiring mechanical ventilation admitted to medical ICUs at UPMC Health Systems hospitals in Western Pennsylvania. Exclusion criteria include inability to obtain informed consent, the presence of tracheostomy, or mechanical ventilation for more than 72 hours before enrollment. The ALIR is approved by the University of Pittsburgh Institutional Review Board (protocol PRO10110387, "ALI Registry and Biospecimen Repository," original approval date: June 17, 2011), and written informed consent is provided by all participants or their surrogates. All research is carried out in accordance with ethical principles outlined in the Declaration of Helsinki.

Patients enrolled in ALIR are classified by consensus of at least three board-certified intensivists (13) into subgroups including: acute respiratory distress syndrome (ARDS) according to the Berlin definition (15); at-risk for ARDS (ARFA) by presence of risk factors without meeting Berlin definition criteria; or as airway controls for those intubated for airway protection in the absence of risk factors and have a normal chest radiograph. Baseline blood samples for ALIR participants are collected within 48 hours of enrollment. For

this study, we performed secondary analyses on 297 participants previously enrolled between 2011 and 2021. We included patients with ARDS and ARFA given the higher occurrence of mortality along with control patients intubated for airway protection who did not have risk factors for ARDS (airway controls). We did not include participants with cardiogenic pulmonary edema as the primary cause of respiratory failure. Participants with COVID-19 were included in this study.

### Clinical Data Collection

Data for demographics, comorbidities, vital signs, outpatient GLP-1 receptor agonist use (liraglutide, semaglutide, and dulaglutide), laboratory values, radiographic reports, and mechanical ventilation parameters are abstracted from the electronic medical record for ALIR participants. Sequential Organ Failure Assessment (SOFA) scores (modified to exclude the neurologic component as Glasgow Coma Scales [GCSs] are not routinely recorded at UPMC and given the challenges in determining GCS in sedated patients) (16) as well as clinical outcomes including survival, ICU length of stay, time to liberation from mechanical ventilation, and 90-day survival are recorded for all participants. Data on several treatments used in the management of ARF including systemic glucocorticoid use, prone positioning, neuromuscular blockade, inhaled pulmonary vasodilatory therapy, and extracorporeal membranous oxygenation during ICU hospitalization were determined as per prior studies (17, 18).

### Assessment of Gastrointestinal Complications

To assess gastrointestinal complications, an additional review of electronic medical records, including nursing documentation and radiology reports, was performed to determine the incidences of gastrointestinal complications using criteria consistent with the Early vs. Delayed Enteral Nutrition (EDEN) trial (19). No prospective assessment for gastrointestinal complications was assessed for this study. Participants having gastrointestinal complications were defined by the incidences of gastric emptying dysfunction, emesis, gut ischemia, or ileus in the first week of study enrollment. Gastric emptying dysfunction was defined by presence of a gastric tube placed on suction or by measured gastric residual volume greater than 400 mL at any time. Gut ischemia classification was based on radiologist interpretation of abdominal imaging tests (CT angiogram of the abdomen, CT abdomen with or without pelvis with contrast, or MRI angiogram of the abdomen). Ileus was similarly defined by radiologist interpretation of abdominal imaging (plain radiography or fluoroscopy of abdomen, CT angiogram of abdomen, CT abdomen with or without contrast, or MRI abdomen).

### Biomarker Assessment

Baseline blood samples are collected within 48 hours of ALIR enrollment and plasma samples are stored at –80 degrees Celsius until biomarker assay. Host response biomarkers, including interleukin (IL)-6, IL-8, receptor for advanced glycation end-products, soluble suppressor of tumorigenicity 2, procalcitonin, pentraxin-3, soluble tumor necrosis factor receptor 1 (sTNFr1), and fractalkine, had been previously determined in the ALIR subset. Circulating incretins (GLP-1, GIP), insulin, and C-peptide levels were determined for this study using Meso Scale Discovery Metabolic U-Plex assay (Meso Scale Discovery, Rockville, MD). Preliminary analyses from our laboratory demonstrated good concordance of incretin levels between samples collected in EDTA tubes and protease-inhibitor containing P800 tubes (Catalog Number 366420; BD Biosciences, San Jose, CA). Circulating markers previously associated with intestinal barrier integrity (intestinal fatty acid-binding protein 2 [FABP2]) (20) and with increased intestinal permeability (lipopolysaccharide-binding protein [LBP] [21] and soluble cluster of differentiation 14 [sCD14]) (22, 23) were determined using enzyme-linked immunosorbent assay (Human FABP2/Intestinal Fatty-Acid Binding Protein Quantikine ELISA Kit; Bio-Techne, Minneapolis, MN) and Luminex (Human Luminex Discovery Assay; Bio-Techne).

### Host Response Subphenotypes

Participants were classified into two host response subphenotypes (hypoinflammatory or hyperinflammatory) using a previously published parsimonious logistic regression model using baseline bicarbonate, sTNFr1, angiopoietin-2, and procalcitonin (24).

### Statistical Analysis

Circulating incretin levels were compared across subgroups of differing illness severity by: 1) clinical classification (ARDS, ARFA, and airway controls) using Kruskal-Wallis test; 2) host response subphenotype using Mann-Whitney *U* test; and 3) survivor status at 90 days by Mann-Whitney *U* test. In our primary analysis, association of each incretin hormone with 90-day mortality was measured using logistic regression. We performed unadjusted analyses for each incretin, and if significant, performed analyses adjusted for age, SOFA score, and circulating IL-6. We chose variables that have plausible relationships with both circulating incretin levels and with mortality. We specifically chose IL-6 due to preclinical studies demonstrating the ability of IL-6 to induce GLP-1 release from enteroendocrine cells (25). In secondary analyses, associations between circulating incretin levels and incidence of any gastrointestinal complication in the first week of enrollment were investigated. Next, to investigate possible pathways connecting incretin hormones and mortality, we investigated associations between circulating incretins and: 1) insulin and C-peptide; 2) biomarkers associated with intestinal health and permeability; and 3) host response biomarkers using Spearman rho. Last, we grouped patients into tertiles based on circulating incretins levels and compared patient characteristics and clinical outcomes by Kruskal-Wallis test or chi-square analysis as appropriate to explore other potential variables contributing to differences in mortality that might not have been included in our prespecified analyses. All analyses were performed with Stata, Version 18 (StataCorp, College Station, TX). Data are reported as median (interquartile range) or *n* (%).

## RESULTS

### Patient Characteristics

Characteristics of patients included in the study are presented in **eTables 1** and **2** (http://links.lww.com/CCX/B495). Our cohort included 120 patients with ARDS, 146 with ARFA, and 31 patients as airway controls.

### GLP-1 Levels Are Increased With Disease Severity

Circulating GLP-1 levels were higher in patients with ARDS (51 pg/mL [22–110 pg/mL]) and ARFA (41 pg/mL [19–91 pg/mL]) compared with airway controls (15 pg/mL [8–31 pg/mL]; $p < 0.01$; **Fig. 1*A***). GIP levels did not differ significantly across clinical groups ($p = 0.20$; **Fig. 1*B***). GLP-1 levels were increased in patients classified into a hyperinflammatory phenotype (117 pg/mL [52–296 pg/mL]) compared with a hypoinflammatory phenotype (29 pg/mL [14–66 pg/mL]; $p < 0.01$; **eFig. 1*A***, http://links.lww.com/CCX/B495), and in nonsurvivors (85 pg/mL [32–190 pg/mL]) compared with survivors (31 pg/mL [15–66 pg/mL]; $p < 0.01$; **Fig. 1*C***). GIP did not differ significantly between host

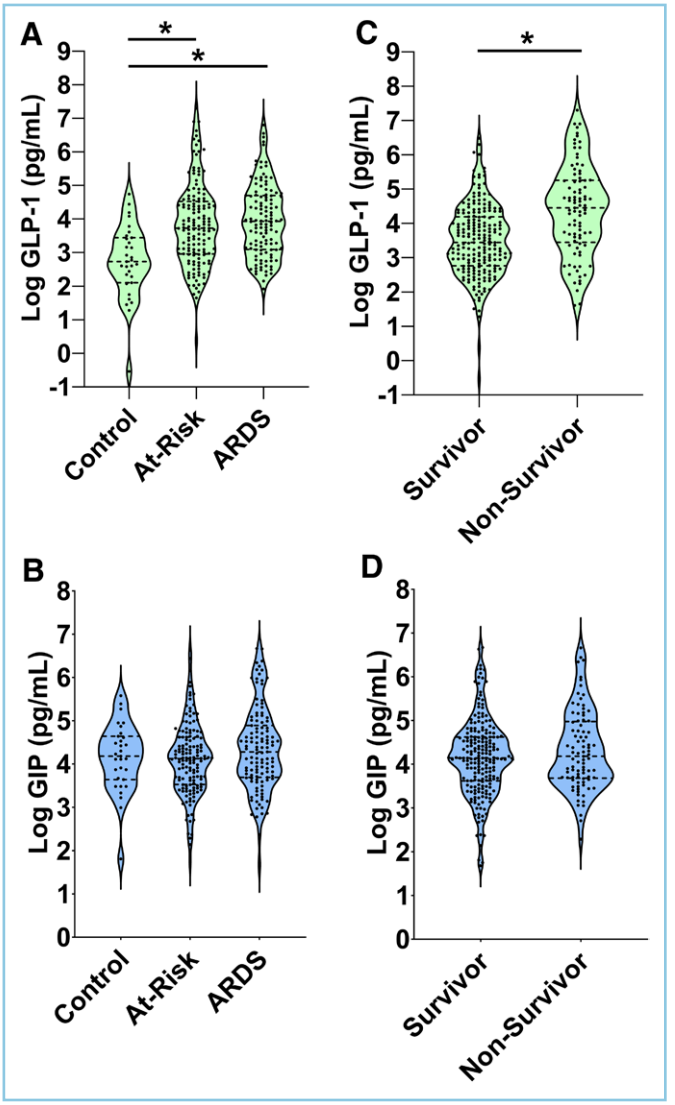


**Figure 1.** Circulating glucagon-like peptide-1 (GLP-1) is increased with disease severity. Circulating GLP-1 on study enrollment is higher (**A**) in participants with or at-risk for acute respiratory distress syndrome (ARDS) compared with airway controls in our study and (**C**) in nonsurvivors compared with survivors at 90 d. In contrast, circulating glucose-dependent insulinotropic peptide (GIP) does not differ significantly between (**B**) clinical groups and (**D**) nonsurvivors and survivors. *Significance at $p < 0.05$.

response subphenotypes ($p$ = 0.07; **eFig. 1*B***, http://links.lww.com/CCX/B495) or between survivors or nonsurvivors ($p$ = 0.39; **Fig. 1*D***). Notably, circulating GLP-1 and GIP were not correlated with each other in our cohort (ρ = 0.05; $p$ = 0.36).

### Patients With Elevated GLP-1 Levels Had More Comorbidities and Required Prolonged Mechanical Ventilation

To explore the observed association of increased GLP-1 with increased mortality, we divided patients into tertiles based on circulating GLP-1 levels (median GLP-1: tertile 1: 13.5 pg/mL [10.1–18.6 pg/mL]; tertile 2: 41.1 pg/mL [30.2–51.6 pg/mL]; tertile 3: 127.8 pg/mL [91.6–246.3 pg/mL]). Compared with patients in the lowest tertile, patients in the highest GLP-1 tertile had a higher BMI (tertile 1: 28.3 [24.6–33.6]; tertile 3: 31.3 [26.7–31.0]; $p$ = 0.05), were more likely to be male (tertile 1: 38 [38%]; tertile 3: 72 [72%]; $p$ < 0.01), and were more likely to have chronic renal failure (tertile 1: 7 [7%]; tertile 3: 17 [17%]; $p$ = 0.03) and chronic liver disease (tertile 1: 3 [3%]; tertile 3: 20 [20%]; $p$ < 0.01) (**Table 1**). Outpatient GLP-1 analog use was low 12 (4.0%) and did not differ significantly across GLP-1 tertiles. No participants received GLP-1 analogs during ICU hospitalization. Patients in the highest GLP-1 tertile had higher severity of illness as evidenced by SOFA scores (tertile 1: 4 [3–6]; tertile 3: 10 [7–11]; $p$ < 0.01), higher prevalence of participants with ARDS or ARFA, higher prevalence of nonpulmonary sepsis, higher use of prone positioning, and higher mechanical ventilation needs including higher PEEP, higher minute ventilation, and higher plateau and driving pressures (Table 1 and **eTable 2**, http://links.lww.com/CCX/B495).

The worse clinical outcomes in tertile 3 were further supported by longer ICU stay (10 d [6–18 d]) and days on mechanical ventilation (7 [4–11]) compared with tertile 2 (9 d [6–16 d] and 7 d [3–12 d], respectively) and tertile 1 (8 d [4–12 d]; $p$ = 0.014 and 4 d [2–10 d]; $p$ < 0.01, respectively) (**eTable 3**, http://links.lww.com/CCX/B495). Finally, our analysis show that patients in tertile 3 had a lower 90-day survival (51 [50%]) compared with patients in tertiles 1 (83 [82%]) and 2 (77 [76%]; $p$ < 0.01; **Fig. 2**).

### Circulating Incretin Hormones Are Not Prognostic of Gastrointestinal Complications

Given the association of GLP-1 with disease severity, we tested for associations between incretins levels and gastrointestinal complications. In our cohort, 98 participants (33%) experienced at least one gastrointestinal complication in the first week after study enrollment—29 (15%) had elevated gastric residuals, 56 (19%) had gastric tubes placed, 16 (5%) had emesis, 36 (12%) had documented ileus on radiographic imaging, and 2 (1%) had imaging findings indicating intestinal ischemia. Neither GLP-1 (unadjusted odds ratio [OR], 1.20 [0.98–1.47]; $p$ = 0.08) nor GIP levels (unadjusted OR, 0.95 [0.72–1.24]; $p$ = 0.69) were associated with gastrointestinal complications.

### Circulating GLP-1 Levels Positively Correlated With Circulating C-Peptide But Not Insulin Levels

We next investigated the relationship of circulating incretins levels with insulin and C-peptide levels. Under physiologic conditions, circulating incretins levels are strongly associated with insulin and C-peptide levels. Circulating insulin levels, contributed by both endogenous secretion and exogenous administration, had a weak positive correlation with GIP (ρ = 0.12; $p$ = 0.03) but not GLP-1 levels ($p$ = 0.10) (**eFig. 2**, http://links.lww.com/CCX/B495). Circulating C-peptide, which reflects the endogenous insulin response, had a stronger positive correlation with GLP-1 (ρ = 0.29; $p$ < 0.01) but not GIP levels ($p$ = 0.26) (eFig. 2, http://links.lww.com/CCX/B495).

### GLP-1 Levels Do Not Correlate With Biomarkers Associated With Intestinal Health and Gut Permeability

Since GLP-1 release might be secondary to injury to the intestinal epithelium, we investigated whether elevation in GLP-1 levels correlated with circulating levels of markers of intestinal health (FABP2) or intestinal permeability (sCD14 and LBP; **Fig. 3**). As expected, sCD14 and LBP levels positively correlated with each other (ρ = 0.54; $p$ < 0.01). sCD14 had modest positive correlations with both GLP-1 (ρ = 0.17; $p$ < 0.01) and GIP levels (ρ = 0.13; $p$ = 0.02), but similar correlations were not observed with LBP levels. Circulating FABP2 levels negatively correlated with sCD14 levels (ρ = –0.24; $p$ < 0.01) but did not significantly associate with the levels of incretin hormones.

## TABLE 1.
## Clinical Characteristics of Participants Separated by Tertiles of Circulating Glucagon-Like Peptide-1

| Variable | Tertile 1 (Lowest) | Tertile 2 (Middle) | Tertile 3 (Highest) | *p* |
|---|---|---|---|---|
| Number of participants | 99 | 99 | 99 | |
| GLP-1 (pg/mL) | 13.5 (10.1–18.6) | 41.1 (30.2–51.6) | 127.8 (91.6–246.3) | < 0.001 |
| Demographics | | | | |
| Age, yr | 57.4 (41.5–67.8) | 58.5 (47.6–71.1) | 63.1 (50.8–69.8) | 0.198 |
| Body mass index | 28.3 (24.6–33.6) | 30.4 (25.9–35.1) | 31.3 (26.7–31.0) | 0.048 |
| Sex, female | 62 (62.6%) | 46 (46.5%) | 28 (28.3%) | < 0.001 |
| Outpatient GLP-1 analog use | 3 (3.0%) | 3 (3.0%) | 6 (6.1%) | 0.609 |
| Comorbidities | | | | |
| Diabetes mellitus | 32 (32.3%) | 43 (43.4%) | 38 (38.4%) | 0.273 |
| Chronic obstructive pulmonary disease | 28 (28.3%) | 19 (19.2%) | 9 (9.1%) | 0.003 |
| Congestive heart failure | 12 (12.1%) | 16 (16.2%) | 17 (17.2%) | 0.577 |
| Chronic renal failure | 7 (7.1%) | 20 (20.2%) | 17 (17.2%) | 0.025 |
| Immunosuppression | 15 (15.2%) | 23 (23.2%) | 26 (26.3%) | 0.145 |
| Chronic liver disease | 3 (3.0%) | 9 (9.1%) | 20 (20.2%) | < 0.001 |
| Pulmonary fibrosis | 3 (3.0%) | 1 (1.0%) | 3 (3.0%) | 0.557 |
| Baseline laboratory values | | | | |
| WBC, cells × 10^9/L | 10.3 (7.8–13.9) | 11.6 (9.1–16.9) | 15.3 (11.4–23.3) | < 0.001 |
| Hemoglobin, g/dL | 11.1 (9.5–12.9) | 10.5 (9.2–12.6) | 10.3 (8.8–12.3) | 0.060 |
| Platelets, cells/mm^3 | 212 (169–261 ) | 195 (138–248 ) | 173 (104–263 ) | 0.027 |
| Creatinine, mg/dL | 0.8 (0.6–1.0) | 1.2 (0.8–1.9) | 1.9 (1.2–3.3) | < 0.001 |
| Bicarbonate, mmol/L | 25 (21–29) | 23 (21–26) | 22 (20–27) | 0.019 |
| Blood urea nitrogen, mmol/L | 14 (10–28) | 27 (19–40) | 45 (28–66) | < 0.001 |
| Severity of illness | | | | |
| Sequential Organ Failure Assessment score | 4 (3–6) | 6.5 (5–8) | 10 (7–11) | < 0.001 |
| Cardiac component | 1 (0–2) | 1 (1–3) | 3 (1–4) | < 0.001 |
| Respiratory component | 3 (2–3) | 3 (2–3) | 3 (2–3) | 0.764 |
| Hepatic component | 0 (0–0) | 0 (0–0) | 0 (0–2) | < 0.001 |
| Renal component | 0 (0–2) | 1 (0–3) | 3 (1–4) | < 0.001 |
| Coagulation component | 0 (0–0) | 0 (0–1) | 0 (0–2) | < 0.001 |
| Baseline ventilatory characteristics | | | | |
| Minute ventilation (L/min) | 9.2 (6.9–10.4) | 10.3 (8.5–11.5) | 10.3 (8.1–13.1) | < 0.001 |
| Positive end-expiratory pressure, cm $H_2O$ | 5 (5–10) | 8 (5–10) | 8 (5–10) | 0.005 |
| Peak inspiratory pressure, cm $H_2O$ | 22 (18–29) | 25 (20–30) | 27 (21–32) | 0.006 |
| Plateau pressure, cm $H_2O$ | 19 (16–23) | 20 (16–25.5) | 22 (19–27) | 0.008 |
| Tidal volume, mL/kg | 6.9 (6.0–7.9) | 7.0 (6.4–7.6) | 6.6 (6.1–7.8) | 0.064 |
| Driving pressure, cm $H_2O$ | 12 (9–15) | 12 (9–15) | 14 (11–17) | 0.022 |
| Compliance, L/cm $H_2O$ | 36 (28–44) | 36 (28–48) | 33 (25–44) | 0.317 |

GLP-1 = glucagon-like peptide-1.

Data are presented as median (interquartile range) or *n* (%) as appropriate. *p* values represent comparisons between tertile groups by Kruskal-Wallis test or chi squared analysis as appropriate.

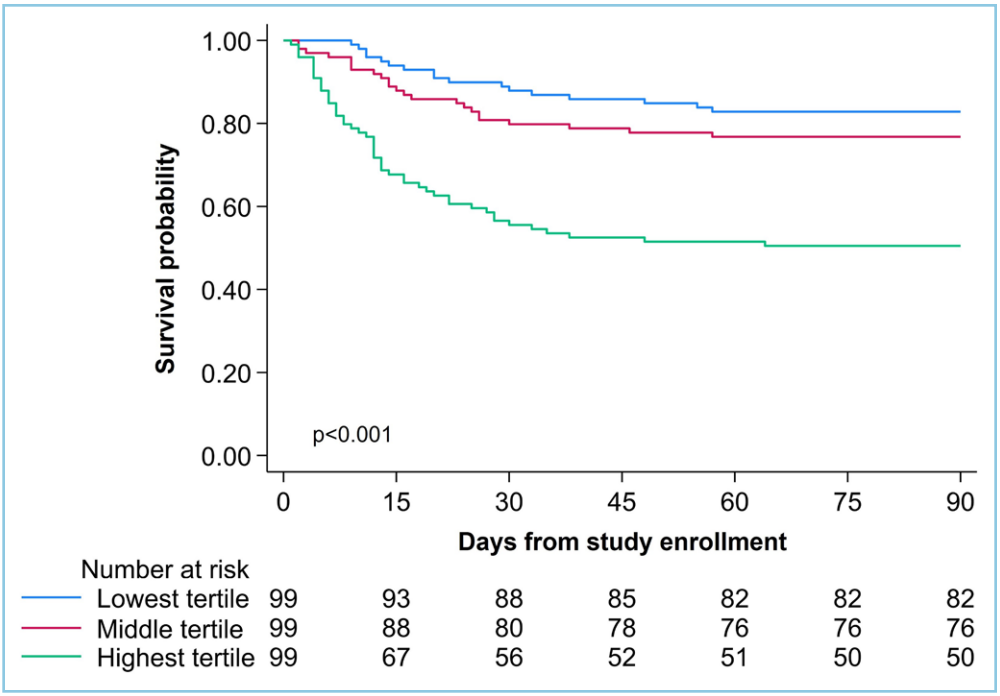


**Figure 2.** Survivorship differs by glucagon-like peptide-1 (GLP-1) tertiles. Unadjusted Kaplan-Meier curves for survival to 90 d following enrollment with at-risk tables are presented by GLP-1 tertile. Participants with the lowest GLP-1 levels (tertile 1) had the highest survival, and participants with the highest GLP-1 levels (tertile 3) had the lowest survival. *p* value represents difference by log-rank test.

### GLP-1 Levels Positively Correlated With Markers of Systemic Inflammation

Next, we investigated relationships between incretins levels and markers of the systemic host response. Circulating GLP-1 levels positively correlated with all measured host response biomarker levels including markers of the innate immunity, endothelial injury, lung epithelial injury, and response to bacterial infections (**Fig. 4**). Accordingly, patients in GLP-1 tertile 3 had the highest levels of systemic inflammation (**eTable 4**, http://links.lww.com/CCX/B495). Circulating GIP levels were not associated with any host response biomarkers in our cohort.

### GLP-1 But Not GIP Is Associated With Increased Mortality

In our primary analysis, we tested for associations between circulating incretin levels and mortality at 90 days, which was 30% in our cohort. In unadjusted analyses, higher GLP-1 levels were significantly associated with increased 90-day mortality (OR, 1.99 [1.55–2.56] for each log unit increase in GLP-1 levels; $p < 0.01$). In contrast, GIP levels were not associated with increased mortality (OR, 1.21 [0.91–1.64]; $p = 0.19$). GLP-1 levels remained significantly associated with increased mortality in analyses adjusted for age, SOFA scores, and circulating IL-6 levels (OR, 2.02 [1.23–3.31]; $p < 0.01$) (**eTable 5**, http://links.lww.com/CCX/B495).

## DISCUSSION

We investigated incretins as prognostic biomarkers in ARF and found that circulating GLP-1 levels were prognostic of increased 90-day mortality independent of age, severity of illness, and circulating IL-6 levels. This phenotype was specific to GLP-1 as circulating GIP levels were not associated with increased mortality in our cohort. Our findings are consistent with prior studies demonstrating endogenous GLP-1 levels as an independent predictor of mortality in acute care settings (4, 8–10) and contrasts other disease states where increasing GLP-1 pharmacologically improves clinical outcomes and decreases mortality (26–30). The association of adverse clinical outcomes specifically with GLP-1 and not GIP contrasts regulation of incretins in physiologic settings where GLP-1 and GIP are increase in concert (31, 32) highlighting unique dissociations of these regulations in critical illness. Our study additionally demonstrates novel associations of GLP-1 with hyperinflammatory states in ARF. To the best of our knowledge, this is the first study to demonstrate a strong association between GLP-1 levels and mortality in patients with ARF.

Consistent with prior clinical studies, in the settings of critical illnesses, our study demonstrates positive correlations between GLP-1 and systemic inflammation (4, 9, 10). However, the upstream regulators of increased GLP-1 during critical illness remain unclear. In preclinical studies, inflammatory cytokines, including IL-6 and IL-1β, have

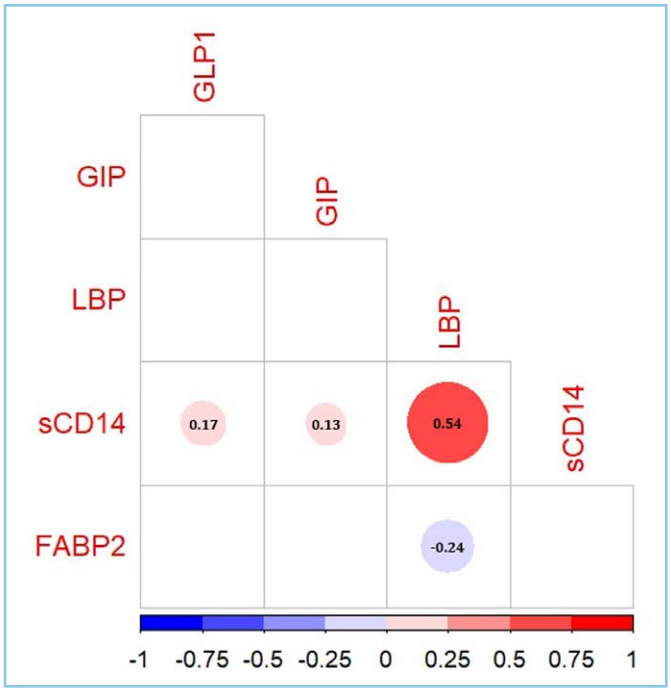


**Figure 3.** Incretins have modest to no significant correlations with markers associated with intestinal health and permeability. Data are presented as a correlogram where *size* and *color* of *circles* denote the direction and magnitude of correlation. Only associations with an adjusted $p < 0.05$ are shown. Soluble cluster of differentiation 14 (sCD14) was positively correlated with both circulating glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), but incretins were otherwise not significantly associated with either fatty acid-binding protein 2 (FABP2) or with lipopolysaccharide-binding protein (LBP) in our cohort. sCD14 was positively correlated with circulating LBP and negatively correlated with circulating FABP2.

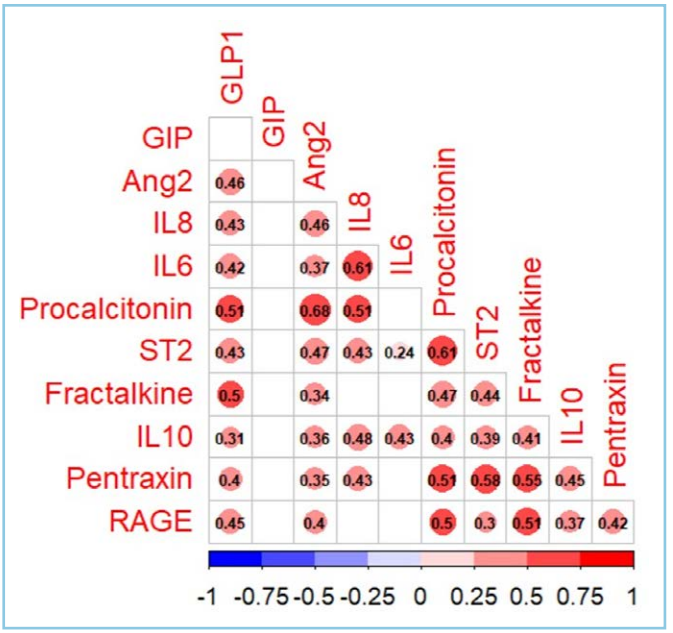


**Figure 4.** Glucagon-like peptide-1 (GLP-1) is positively correlated with circulating markers of the systemic host immune response. *Size* and *color* of *circles* denote the direction and magnitude of correlation. Only associations with an adjusted $p < 0.05$ are shown. Circulating GLP-1 was positively correlated with all tested markers of the systemic host response. Glucose-dependent insulinotropic peptide (GIP) did not demonstrate any significant associations with host response biomarkers or with GLP-1. Ang2 = angiopoietin-2, IL = interleukin, RAGE = receptor for advanced glycation end-products, ST2 = suppressor of tumorigenicity 2.

been found to promote release of incretins from enteroendocrine cells potentially in response to disruption of gut barrier integrity (25, 33, 34). Release of GLP-1 in response to inflammatory stimuli may reflect an effort by the host to limit further intestinal injury or decrease local or systemic inflammation through anti-inflammatory effects of incretin hormones (35–38). Thus, the proportional increases in GLP-1 with increased disease severity and increased mortality risk may reflect increased intestinal insult and an increased counter-response, which may not be sufficient to overcome the dysregulated immune system in critical illness. To support this notion, in preclinical models of sepsis and acute lung injury, exogenous incretins exert benefits in decreasing endothelial injury, lung inflammation, edema, and injury, and reducing mortality (35, 36, 39, 40). While clinical studies have been conducted to test the therapeutic potential of incretins for promoting euglycemia in critical illness (41, 42), additional studies are needed to investigate therapeutic benefits of GLP-1 in improving clinical outcomes from critical illness, especially respiratory failure.

We performed additional analyses to identify other possible mechanisms to explain the relationship between GLP-1 and mortality. When comparing patients in the highest GLP-1 tertile who had the highest mortality to patients in the lowest tertile with the lowest mortality, we found that the patients in the highest GLP-1 tertile were older, more likely to be male, had a higher prevalence of chronic liver disease, and higher illness severity as evidenced by higher SOFA scores, and increased ventilatory support. We hypothesized that the higher illness severity may contribute to increased rates of intestinal injury but found only modest correlations between GLP-1 and a single marker associated with intestinal permeability, sCD14, and did not find associations of GLP-1 with gastrointestinal complications. The lack of association with gastrointestinal complications may be attributed to bias in recording

gastrointestinal complications and limited number of patients for whom the data are available.

We acknowledge a few limitations of this study. First, active GLP-1 in circulation has a short half-life (approximately 1–2 min) due to rapid degradation by dipeptidyl peptidase 4. Our study measured both active and inactive forms of GLP-1 to help overcome this limitation, but additional studies are needed to better characterize incretin kinetics in critical illness (43). Second, the biomarkers we used to assess intestinal permeability, such as LBP and sCD14, may not be specific and can increase with other aspects of the host response. Better biomarkers are needed to assess the intestinal health in critical illness (44). Third, assessment for gastrointestinal complications was not prospectively standardized. Prior studies have suggested incretins as being prognostic of delayed enteral nutrition target achievement in pediatric critical care (45); however, limited data are available in adult populations. Fourth, outpatient GLP-1 analog use was low in our cohort given the time period of study enrollment, and future studies may need to consider the effects of outpatient GLP-1-based therapeutics on circulating levels and clinical outcomes given increasing use of these drugs for weight loss (46). Last, our study represents findings from a single center; while our results are consistent with other studies reported in other forms of critical illness, some findings may be underpowered. Better understanding of GLP-1 in respiratory failure is warranted to improve patient outcomes.

## CONCLUSIONS

Circulating GLP-1 was prognostic of increased mortality in a cohort of critically ill adult patients with ARF. GLP-1 increased in concert with increased disease severity and positively correlated with markers of the systemic host immune response. We propose that GLP-1 levels can serve as a biomarker to identify patients with ARF who have an increased risk of worsening disease severity and mortality. Further studies of incretin hormones and intestinal pathways in critical illness are needed to validate the findings made in this study in additional cohorts and to determine causal pathways contributing to increased mortality.

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*Drs. Hansell and Shah were involved in concept and design. Drs. Hansell, Aneis, and Malik were involved in data collection. Ms. Zhao, Drs. Prendergast, and Zhang were involved in performance of molecular assays. Drs. Hansell and Shah were involved in statistical analysis. Drs. Hansell, Aneis, Kitsios, Bain, Suber, Evankovich, Sharma, Ramakrishnan, Prendergast, Hensley, Malik, Patel, Nouraie, Dela Cruz, McVerry, Zhang, and Shah were involved in analysis and interpretation of data. Drs. Hansell and Shah were involved in drafting of initial version of article. Drs. McVerry and Shah were involved in obtained funding. Dr. Shah was involved in supervision. All authors provided critical revisions to the article and gave their approval to the submission of this article.*

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