의학석사 학위논문

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**A thesis of the Degree of Master of Philosophy**

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# Effect of preadmission metformin use on clinical outcome of ARDS among critically ill patients with diabetes

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# ABSTRACT

**Introduction:** Acute respiratory distress syndrome (ARDS) is related to high mortality and morbidity and is a major concern for critically ill patients, but there are currently no proven therapeutic measures to improve the clinical course of ARDS, except low tidal volume ventilation. Metformin is known to have pleiotropic effects including anti-inflammatory activity. In animal studies, metformin attenuated the severity of acute lung injury. Therefore, we hypothesized that preadmission metformin, which can show an anti-inflammatory effect, might alter the progress of ARDS among intensive care unit (ICU) patients with diabetes mellitus (DM).

**Methods:** We performed a retrospective cohort study of patients who were admitted to the medical ICU at Seoul National University Hospital because of ARDS from January 1, 2005 to April 30, 2015, and reviewed ARDS patients with DM. Metformin use was defined as prescribed within 3 months before admission. We analyzed 30-day mortality and severity of ARDS including PaO2/FiO2 ratio, lung injury score (LIS) and lung compliance after propensity score matching.

**Results:** Of 558 patients diagnosed as ARDS, 128 (23.3%) patients had diabetes and only 3 patients were treated with metformin monotherapy. Thirty patients received metformin in combination with other antidiabetic medications. Demographic characteristics, cause of ARDS, and comorbid conditions except chronic kidney disease were not different between metformin users and nonusers. Ventilator demand, hypoxemia index, extent of alveolar consolidation, and LIS were similar in both groups. The 30-day mortality was 42.42% in metformin users and 55.32% in metformin nonusers. On multivariable regression analysis, use of metformin showed trends to reduce a 30-day mortality, but this was not significant (adjusted β-coefficient –0.19, 95% CI –1.76 to 1.39, P = .816). Propensity-score-matched analyses showed similar results.

**Conclusions:** Preadmission metformin use was not associated with reduced 30-day mortality among ARDS patients with DM in our medical ICU.

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**Keywords:** Acute respiratory distress syndrome; diabetes mellitus; metformin; clinical outcome

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# LIST OF ABBREVIATIONS

APACHE II score: Acute Physiology and Chronic Health Evaluation II score
ARDS: acute respiratory distress syndrome
BIPAP: bilevel positive airway pressure
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
DM: diabetes mellitus
DBP: diastolic blood pressure
DPP-IV inhibitor; dipeptidyl peptidase-4 inhibitor
FiO2: fraction of inspired oxygen
HbA1c: glycated hemoglobin
HR: heart rate
ICU: intensive care unit
IPF: idiopathic pulmonary fibrosis
LIS: lung injury score
NO: nitric oxide
PaO2: partial pressure of oxygen in arterial blood
PEEP: positive end expiratory pressure
PIP: peak inspiratory pressure
RR: respiratory rate
RRT; renal replacement therapy
SBP: systemic blood pressure
SOFA score: Sequential Organ Failure Assessment score
V-V ECMO: veno-venous extracorporeal membrane oxygenation

# INTRODUCTION

Acute respiratory distress syndrome (ARDS) is known as an acute systemic syndrome of lung inflammation characterized by increased permeability, which can result in severe hypoxia. This syndrome is of major concern for critically ill patients with increasing morbidity and mortality.(1) Mortality from ARDS is expected to be approximately 40–50%.(1, 2) Although inflammation is known to be involved in the pathogenesis of ARDS, several anti-inflammatory drugs have failed to improve ARDS outcomes. Until now, the only proven treatment modality to improve the clinical course of ARDS is low tidal volume ventilation.(1, 3, 4)

Interestingly, several clinical studies found that diabetic patients develop ARDS less frequently than nondiabetic patients do.(5, 6) Diabetes is regarded as a protective factor against the development of ARDS, even after adjustment for confounders such as age or severity of illness.(7) It is thought that diabetes mellitus (DM) may be involved in pathogenesis of ARDS and alter its development by altering immune system and inflammatory responses, such as adherence of neutrophils to the endothelium or bactericidal activity of inflammatory cells.(8-10)

The biguanide, metformin, is a widely used antidiabetic drug for the treatment of type 2 DM and recommended to newly diagnosed diabetes patients who have no contraindications for the drug.(11-13) It is well known that in addition to its glucose-lowering effect and enhancement of insulin sensitivity, metformin has pleiotropic effects such as anti-inflammatory, antioxidant, endothelial barrier-enhancing, and antithrombotic effects.(14-16)

Experimental animal models of acute lung injury showed that pretreatment with metformin preserves alveolar capillary permeability; therefore, metformin decreases the severity of acute lung injury in high-pressure ventilation.(17) A few human studies have examined the effect of metformin in critically ill patients. One of these studies found that when metformin was added to intensive insulin therapy in intensive care unit (ICU) patients, decreased levels of inflammatory cytokines were found.(18) In diabetes patients who underwent cardiac surgery, preadmission metformin use decreased postoperative morbidity by more than 50% and led to a substantial decrease in mortality.(19) In a population-based cohort study, preadmission metformin use reduced 30-day mortality among medical and surgical ICU patients with diabetes.(20)

However, it is not known whether metformin can have a favorable effect on patients with ARDS. We assumed that the benefits of

metformin, including glucose-lowering and pleiotropic effects, such as anti-inflammatory effects, may have a protective effect on the clinical outcome of ARDS. We hypothesized that preadmission use of metformin for diabetes patients attenuates the severity of ARDS, and may furthermore improve the outcome of these patients.

# MATERIALS AND METHODS

## 1. Patients eligibility

We retrospectively reviewed the medical records of patients who were admitted to the medical ICU at Seoul National University Hospital between January 1, 2005 to April 30, 2015. We included only adult patients (19 years of age or older) who underwent mechanical ventilation and were clinically diagnosed as having ARDS according to the newly revised Berlin definition.(1) We identified type 2 diabetes among the ARDS patients by using an algorithm with high certainty, incorporating any previous in- or outpatient records for clinical diagnosis of diabetes, any filled prescription for an antidiabetic drug or a glycated hemoglobin A1c (HbA1c) level of 6.5% or more within 3 months of the admission to the ICU.(11)

Demographic characteristics, laboratory findings, preadmission antidiabetic drug usage for DM, severity of illness, ventilator setting, interventions conducted in the ICU, and clinical courses between the two groups were reviewed. We excluded patients who were clinically diagnosed as having ARDS, but who were not mechanically ventilated for various reasons, such as refusal of any invasive procedure including intubation. Mechanical ventilation depends on patients or their legal representative's will or application of noninvasive ventilation. In addition, we excluded patients who died within 48 hours after ICU admission.

This study was conducted in compliance with the Declaration of Helsinki (2015) and the Institutional Review Board Committee of our hospital exempted the need for informed consent because of the retrospective nature of the medical record review and anonymity of reporting.

## 2. Definition of preadmission metformin use

For each patient, we identified all prescriptions for antidiabetic drugs within 3 months preceding admission. Prescription data were obtained from the Seoul National University Hospital electronic medical record database, or identified from medications prescribed at other hospitals, which were taken until a day before admission. We defined metformin users as those who have taking metformin within 3 months before ICU admission; other ICU patients with diabetes were defined as metformin nonusers. Metformin users include those with metformin monotherapy and combination therapy with other antidiabetic drugs.

## 3. Severity of ARDS

Severity of hypoxemia was classified as mild, moderate, or severe according to the Berlin definition.(1) In addition to the Berlin level of ARDS severity, we considered other clinical factors for the severity index of ARDS including lung injury score (LIS), degree of alveolar consolidation on chest radiograph, lung compliance, time to intubation, and mechanical ventilation.

The LIS is composed of four components: (1) chest roentgenogram score; (2)

hypoxemia score; (3) positive end-expiratory pressure (PEEP) score; and (4) respiratory system compliance score, in which each component was categorized from 0 to 4 with the higher score as worse.(21) The total LIS was calculated by dividing the sum of each component score by the number of components used. The LIS is classified as no lung injury (0 point), mild-to-moderate lung injury (0.1–2.5 points), and severe lung injury (>2.5 points).(17) For LIS, static compliance of the respiratory system is used, but it has a restricted application in retrospective study. Therefore, we supplemented dynamic lung compliance as a secondary outcome as an alternative evaluation of ARDS severity.

We utilized a bedside chest radiograph instead of computed tomography (CT) for evaluation of alveolar consolidation reflecting ARDS severity because it is difficult to obtain chest CT from all ARDS patients.

## 4. Outcome measure

We measured clinical outcomes of ARDS patients with diabetes depending on usage of metformin including a 30-day mortality, ventilator-free days, ICU-free days, indicators of severity of ARDS including partial pressure of oxygen in arterial blood (PaO2)/fraction of inspired oxygen (FiO2) ratio, LIS, time to intubation and mechanical ventilation, and lung compliance.

## 5. Statistical analyses

Statistical tests were performed with STATA software (version 13.1; StataCorp, College Station, TX, USA). A $\chi 2$ test for comparison of categorical variables and a Student t test for continuous variables were applied. We performed univariable and thereafter multivariable logistic linear regression analysis with adjustment by confounders that had $P < .10$ in the univariable analysis and usage of metformin. A propensity score was derived from a logistic regression model used as a dichotomous dependent variable and associated covariates. There were few patients in the metformin use group; therefore, we performed an exact logistic regression analysis and used Firth's penalized-likelihood approach to compensate for the small sample size when we analyzed the propensity-matched cohort. We used a Kaplan–Meier curve to analyze survival between the group treated with metformin and the group treated with other antidiabetic drugs except metformin. $P < .05$ was considered significant.

# RESULTS

A flow diagram for the study is presented in Figure 1. Among 558 patients who met the Berlin definition of ARDS, 128 (23.3%) had diabetes. Among ARDS patients with diabetes, only 3 patients were treated with metformin monotherapy for diabetic control, 30 patients used combination treatment, and other antidiabetic medications except metformin were prescribed to 69 patients. Twenty-six patients did not use any antidiabetic medications because of favorably controlled diabetes or unawareness of diabetes until admission. Among the combination treatment group including metformin, 14 (46.7%) patients were treated with metformin and sulfonylurea, 7 (23.3%) with metformin and dipeptidyl peptidase-4 inhibitor, and 8 (26.7%) with more than the triple combination regimen, respectively. We divided patients into two groups: metformin users and metformin nonusers comprising patients who were treated with other antidiabetic drugs except metformin and untreated patients.

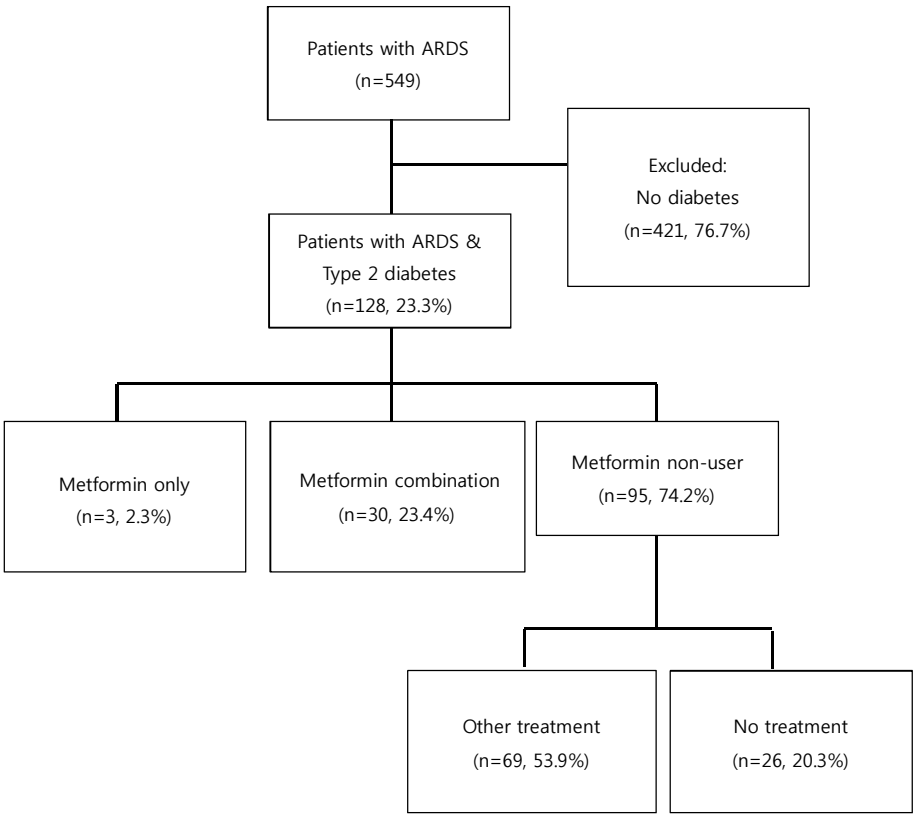



Figure 1. Study flow

The baseline characteristics of all 128 patients who were clinically diagnosed as having ARDS with diabetes are shown in Table 1. Mean age was 69.8 years and 72.7% of metformin users were male. The mean time interval between hospital admission and ICU admission was 8.9 days for metformin users and 7.7 days for nonusers. The most common cause of ARDS was direct lung injury, such as caused by pneumonia in both groups. The comorbidity conditions were not significantly different between the groups. Only numbers of patients with chronic kidney disease who had undergone or were contemplating renal replacement therapy were significantly high among metformin nonusers.

| | All ARDS patients with type 2 diabetes mellitus (n=128) | | P value | Propensity matched cohort | | P value |
|---|---|---|---|---|---|---|
| | Metformin users (n=33) | Metformin nonusers (n=95) | | Metformin users (n=33) | Metformin nonusers (n=33) | |
| Age, yr, mean(SD) | 69.79(11.38) | 66.59(9.63) | 0.120 | 69.79(11.38) | 69.42(11.20) | 0.896 |
| Sex, male(n, %) | 24(72.73) | 76(80.00) | 0.384 | 24(72.73) | 23(69.70) | 0.786 |
| BMI, mean(kg/$m^2$, SD) | 22.81(3.40) | 22.10(3.94) | 0.360 | 22.81(3.40) | 22.53(3.64) | 0.747 |
| Days before ICU admission (days, SD) | 8.88(16.20) | 7.73(18.36) | 0.750 | 8.88(16.20)) | 10.12(22.48) | 0.798 |
| CPR before ICU admission (n,%) | 2(6.06) | 6(6.32) | 0.958 | 2(6.06) | 2(6.06) | 1.000 |
| **Cause of ARDS (n, %)** | | | | | | |
| direct lung injury | 25(75.76) | 72(75.79) | | 25(75.76) | 25(75.76) | |
| Non-direct lung injury | 8(24,24) | 23(24.21) | 0.829 | 8(24.24) | 8(24.24) | 0.146 |
| **Comorbidities (n, %)** | | | | | | |
| Hypertension | 17(51.52) | 48(50.53) | 0.922 | 17(51.52) | 14(42.42) | 0.459 |
| Ischemic heart disease | 7(21.21) | 21(22.11) | 0.915 | 7(21.21) | 7(21.21) | 1.000 |
| Arrhythmia | 10(30.30) | 16(16.84) | 0.098 | 10(30.30) | 6(18.18) | 0.251 |
| Chronic pulmonary disease | 11(33.33) | 28(29.47) | 0.678 | 11(33.33) | 6(18.18) | 0.159 |
| Cerebrovascular disease | 5(15.15) | 21(22.11) | 0.392 | 5(15.15) | 8(24.24) | 0.353 |
| Liver cirrhosis | 1(3.03) | 6(6.32) | 0.475 | 1(3.03) | 3)9.09) | 0.302 |
| History of cancer | 4(12.12) | 12(12.63) | 0.939 | 4(12.12) | 3(9.09) | 0.689 |
| Metastatic cancer | 9(27.27) | 19(20.00) | 0.384 | 99(27.27) | 7(21.21) | 0.566 |
| Hematologic malignancy | 4(12.12) | 11(11.58) | 0.934 | 4(12.12) | 5(15.15) | 0.720 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Chronic kidney disease | 1(3.03) | 21(22.11) | 0.012 | 1(3.03) | 9(27.27) | 0.006 |
| Immunosuppressed§ | 8(24.24) | 2(28.42) | 0.643 | 8(24.24) | 8(24.24) | 1.000 |

ARDS, acute respiratory distress syndrome; BMI, body mass index; CPR, cardiopulmonary resuscitation; ICU, intensive care unit;

§ Patients who has hematologic malignancy, neutropenia and taking immunosuppressant because of autoimmune disease or posttransplant GVHD prophylaxis were defined as immunosuppressed.(22)

Table 1. Demographic characteristics of enrolled patients

Clinical characteristics on the first day of ICU admission are presented in Table 2. Vital signs including blood pressure, heart rate, respiratory rate, and body temperature did not show intergroup differences depending on metformin use. Acute Physiology and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were not significantly different from those for patients with or without metformin use (APACHE II: 31.79 ± 8.73 vs 30.97 ± 7.57; P = .61; SOFA: 9.88 ± 4.22 vs 9.62 ± 3.46; P = .73). The quality of blood glucose control was assessed by initial glucose level before insulin administration at the time of ICU admission and HbA1c (Table 2). Although the mean initial blood glucose level was significantly higher in metformin users (251.9 ± 98.1 vs 210.3 ± 89.3; P = .03), the mean HbA1c was not different between the groups (7.3 ± 1.0 vs 7.3 ± 1.5; P = .84). To compare the severity of systemic inflammation, inflammatory markers including C-reactive protein (CRP), white blood cell count, and lactic acid were reviewed; however, there was no significant difference between the two groups (Table 2).

The respiratory parameters including initial ventilator setting are presented in Table 2. At the ICU admission, initial ventilator setting was not different between the two groups. A large proportion of patients (>80%) had mild-to-moderate ARDS severity, and the severity was not significantly different between the groups. At the time of clinical diagnosis of ARDS, mean quadrant alveolar consolidation on chest radiographs (2.8 ± 0.8 vs 2.9 ± 0.9; P = .88) and mean LIS calculated by using 3 determinants, which were alveolar consolidation in chest radiograph, PEEP score, and hypoxemia score, except for respiratory system compliance score (2.2 ± 0.5 vs 2.2 ± 0.7; P = .95) were similar in both groups. Despite the significantly short time between initiation of mechanical ventilation and nitric oxide (NO) use in metformin users (0.7 ± 1.5 vs 8.2 ± 7.6 days; P = .00), there were only a small number who used NO (30.3 vs 31.6%; P = .89). We also assessed the utility of venovenous extracorporeal membrane oxygenation (VV-ECMO), but only 3 metformin users and 6 nonusers were identified and there was no significant difference between them.

| | All ARDS patients with type 2 diabetes mellitus (n=128) | | P value | Propensity matched cohort | | P value |
|---|---|---|---|---|---|---|
| | Metformin users (n=33) | Metformin nonusers (n=95) | | Metformin users (n=33) | Metformin nonusers (n=33) | |
| **Severity of illness (mean, SD)** | | | | | | |
| APACHE II score | 31.79(8.73) | 30.97(7.57) | 0.608 | 31.79(8.73) | 31.94(8.93) | 0.945 |
| SOFA score | 9.88(4.22) | 9.62(3.46) | 0.729 | 9.88(4.22) | 9.39(3.56) | 0.616 |
| **Glycemic control (mean, SD)** | | | | | | |
| blood glucose level, mg/dL | 251.94 (98.12) | 210.31 (89.34) | 0.028 | 251.94 (98.16) | 219.18 (99.97) | 0.187 |
| HbA1c, % | 7.275(0.99) | 7.34(1.45) | 0.843 | 7.28(0.99) | 7.19(1.42) | 0.831 |
| **Laboratory test (mean , SD)** | | | | | | |
| WBC ($x10^3/\mu\ell$) | 14.10(9.75) | 12.48(7.16) | 0.310 | 14.10(9.75) | 13.44(6.23) | 0.743 |
| Hb (g/dL) | 10.58(1.98) | 10.25(1.99) | 0.404 | 10.58(1.98) | 10.22(2.30) | 0.501 |
| Platelet ($x10^3/\mu\ell$) | 211.30 (128.20) | 191.74 (124.73) | 0.442 | 211.30 (128.20) | 232.12 (151.45) | 0.549 |
| CRP (mg/dL) | 18.17(10.05) | 16.21(10.14) | 0.344 | 18.17(10.05) | 13.41(8.36) | 0.041 |
| Lactic acid (mg/dL) | 3.60(2.52) | 2.93(2.62) | 0.373 | 3.60(2.52) | 4.01(3.78) | 0.714 |
| **Initial Ventilator settings, mean (SD)** | | | | | | |
| PEEP (cm H2O) | 6.24(2.66) | 6.61(2.24) | 0.440 | 6.24(2.66) | 6.45(2.00) | 0.715 |
| Driving pressure (cm H2O) | 19.55(4.66) | 18.73(4.49) | 0.378 | 19.55(4.66) | 19.12(4.95) | 0.721 |
| PIP, cm H2O | 26.19(4.65) | 26.43(4.69) | 0.805 | 26.19(4.65) | 26.28(5.36) | 0.941 |
| Tidal volume (mL) | 447.76 (148.55) | 468.29 (140.62) | 0.478 | 447.76 (148.55) | 447.06 (130.18) | 0.984 |
| FiO2 (%) | 83.09(21.99) | 80.91(19.44) | 0.592 | 83.09(21.99) | 81.70(19.70) | 0.787 |
| Minute ventilation (L/min) | 10.41(3.46) | 10.39(3.85) | 0.976 | 10.41(3.46) | 9.61(3.86) | 0.388 |
| **Hypoxemia index (PaO2/FiO2 ratio)** | | | | | | |
| Mild, n (%) | 19(57.58) | 42(44.21) | | 19(57.58) | 15(45.45) | |
| Moderate, n (%) | 11(33.33) | 41(43.16) | 0.414 | 11(33.33) | 14(42.42) | 0.615 |
| Severe, n (%) | 3(9.09) | 12(12.63) | | 3(9.09) | 4(12.12) | |
| Dynamic compliance, ml/cm H2O | 23.66(9.11) | 25.57(20.37) | 0.611 | 23.66(9.11) | 27.41(32.38) | 0.532 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Alveolar consolidation, quadrant ,n (SD) | 2.84(0.77) | 2.87(0.93) | 0.876 | 2.84(0.77) | 2.76(0.94) | 0.687 |
| Lung injury score, mean(SD) | 2.23(0.53) | 2.22(0.65) | 0.951 | 2.23(0.53) | 2.20(0.62) | 0.831 |

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CRP, C-reactive protein; FiO2, fraction of inspired oxygen; Hb, hemoglobin; HbA1c, Glycated hemoglobin; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; SOFA score, Sequential Organ Failure Assessment score; WBC, white blood cells

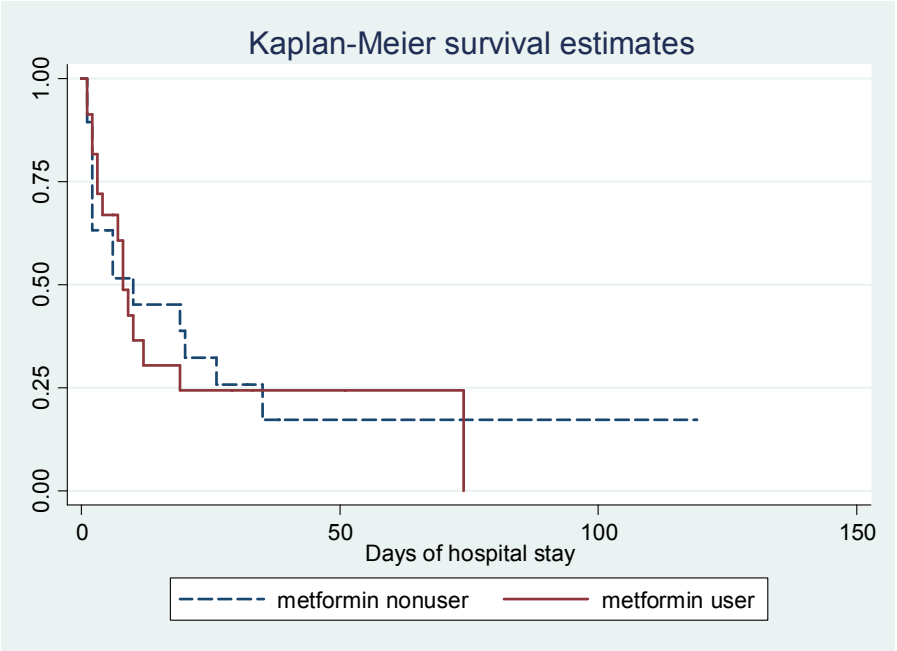
Table 2. Severity of illness and respiratory parameters at the time of intensive care unit admission

Among 128 ARDS patients with DM, 89(69.5%) patients died and 39(30.5%) survived during hospital stay. Use of metformin did not significantly reduce the risk of in-hospital mortality in patients with ARDS (OR 0.69, 95% CI, 0.30-1.61, p=.394). The 30-day mortality was higher in metformin nonusers than users (14 of 33 patients vs 52 of 95 patients; P = .20), but this was not significant (Table 3, Figure 2). We also analyzed 60- and 90-day mortality, but the results were similar. At 30 days since ICU admission, mean ventilator-free days (19.9 ± 6.5 vs 18.4 ± 7.2; P = .33) and mean ICU-free days (17.2 ± 7.1 vs 16.1 ± 7.5; P = .53) were not significantly different between metformin users and nonusers. The mean total length of stay in hospital tended to be longer in nonusers (47.8 ± 54.8 vs 54.8 ± 104.3 days; P = .60) than users, but the difference was not significant.

| | All ARDS patients with type 2 diabetes mellitus (n=128) | | P value | Propensity matched cohort | | P value |
|---|---|---|---|---|---|---|
| | Metformin users (n=33) | Metformin nonusers (n=95) | | Metformin users (n=33) | Metformin nonusers (n=33) | |
| **Mortality, n (%)** | | | | | | |
| 30 days | 14(42.42) | 52(55.32) | 0.202 | 14(42.42) | 18(56.25) | 0.265 |
| 60 days | 20(60.61) | 63(67.02) | 0.505 | 20(60.61) | 21(65.63) | 0.675 |
| 90 days | 21(63.64) | 67(71.28) | 0.413 | 21(63.64) | 22(68.75) | 0.663 |
| **Ventilator-free days, mean (SD)** | | | | | | |
| day 1 to 30 | 19.89(6.54) | 18.41(7.18) | 0.333 | 19.89(6.54) | 18.10(6.64) | 0.322 |
| day 1 to 60 | 46.44(11.40) | 46.47(10.80) | 0.988 | 46.44(11.40) | 46.65(10.69) | 0.941 |
| **ICU-free days, mean (SD)** | | | | | | |
| day 1 to 30 | 17.15(7.08) | 16.10(7.48) | 0.528 | 17.15(7.08) | 15.83(6.84) | 0.483 |
| day 1 to 60 | 41.88(13.33) | 42.51(11.79) | 0.799 | 41.88(13.33) | 41.82(13.17) | 0.986 |
| Total hospital stay, mean (SD) | 47.82(54.81) | 54.77(104.28) | 0.602 | 47.82(54.81) | 61.73(90.05) | 0.451 |
| NO use, n(%) | 10(30.30) | 30(31.58) | 0.892 | 10(30.30) | 11(33.33) | 0.792 |
| Time to NO gas, days, mean(SD) | 0.7(1.49) | 8.23(7.62) | 0.004 | 0.7(1.49) | 8.11(9.14) | 0.021 |
| **Intervention in ICU, N (%)** | | | | | | |
| V-V ECMO | 3(9.09) | 6(6.32) | 0.591 | 3(9.09) | 3(9.09) | 1.000 |
| RRT | 10(30.30) | 32(33.68) | 0.722 | 10(30.30) | 10(30.30) | 1.000 |
| Tracheostomy | 10(30.30) | 24(25.26) | 0.572 | 10(30.30) | 10(30.30) | 1.000 |
| BIPAP apply | 4(12.12) | 10(10.53) | 0.800 | 4(12.12) | 3(9.09) | 0.689 |
| ICU Readmission | 3(9.68) | 9(9.68) | 1.000 | 3(9.68) | 6(18.18) | 0.328 |

BIPAP, bilevel positive airway pressure; NO, nitric oxide; RRT, renal replacement therapy; V-V ECMO, veno-venous extracorporeal membrane oxygenation

Table 3. Clinical outcomes according to metformin use




The 30-day mortality was lower in metformin users than nonusers (42.42% vs. 55.32%; P = .202) and similar result was shown in propensity matched cohort (42.42% vs. 56.25%; p=.265)

Figure 2. The effect of preadmission metformin on 30-days mortality of ARDS patients with diabetes

The relationship between 30-day mortality and the clinical parameters was modeled using univariable and subsequent multivariable logistic regression. The odds ratios (ORs) of death within 30 days of ICU admission are presented in Table S1, which includes not only data with P < .10 in the univariable analysis, but also assumed that clinical factors could influence the outcome. A propensity score was derived from the logistic regression model, including age and sex. On multivariable analysis with covariates in propensity-score-matched cohort, we also performed Firth's penalized likelihood approach to compensate for the small sample size. In an unmatched cohort, immunosuppressed patients and high serum lactic acid level were significantly related to 30-day mortality (β-coefficient 2.40, 95% confidence interval (CI) 0.31 to 4.50, P = .025; β-coefficient 0.60, 95% CI 0.10 to 1.10, P = .018, respectively) (Table S2), but not in the propensity-score-matched cohort (β-coefficient 2.63, 95% CI –1.06 to 6.31, P = .162 and β-coefficient –0.05, 95% CI –0.81 to 0.71, P = .897, respectively) (Table 4). Neither in the unmatched cohort nor the propensity matched cohort, was there any significant association between treatment with metformin and 30-day mortality.

| | Unmatched cohort | | | Propensity matched cohort | | |
|---|---|---|---|---|---|---|
| | Odds ratio | 95% confidence interval of OR | P value | Odds ratio | 95% confidence interval of OR | P value |
| Days before ICU admission | 0.99 | 0.97-1.01 | 0.292 | 0.98 | 0.95-1.01 | 0.261 |
| BMI | 1.14 | 1.03-1.27 | 0.013 | 1.26 | 1.05-1.50 | 0.011 |
| Hypertension | 0.80 | 0.40-1.60 | 0.527 | 0.44 | 0.16-1.20 | 0.108 |
| Cerebrovascular disease | 0.36 | 0.14-0.90 | 0.029 | 0.46 | 0.12-1.66 | 0.230 |
| Metastatic cancer | 2.34 | 0.96-5.66 | 0.061 | 1.45 | 0.47-4.53 | 0.519 |
| Chronic kidney disease | 0.58 | 0.29-1.48 | 0.257 | 0.38 | 0.09-1.64 | 0.197 |
| Immunosuppressed | 3.11 | 1.34-7.21 | 0.008 | 4.35 | 1.23-15.44 | 0.023 |
| HR at ICU admission | 1.02 | 1.01-1.04 | 0.008 | 1.03 | 1.07-1.06 | 0.010 |
| RR at ICU admission | 1.04 | 0.99-1.10 | 0.128 | 1.04 | 0.97-1.12 | 0.235 |
| pH | 0.37 | 0.02-7.51 | 0.519 | 0.03 | 0.00-2.37 | 0.118 |
| HCO3 | 1.01 | 0.94-1.08 | 0.879 | 0.91 | 0.79-1.04 | 0.149 |
| Hb | 1.18 | 0.98-1.42 | 0.086 | 1.39 | 1.03-1.86 | 0.029 |
| Lactic acid | 1.53 | 1.05-2.22 | 0.028 | 1.61 | 1.06-2.44 | 0.026 |
| PEEP | 1.04 | 0.89-1.20 | 0.640 | 1.34 | 1.05-1.72 | 0.019 |
| FiO2 | 1.02 | 1.00-1.03 | 0.094 | 1.02 | 0.99-1.05 | 0.202 |
| Lung injury score | 1.35 | 0.76-2.40 | 0.302 | 2.24 | 0.89-5.63 | 0.087 |
| Metformin use | 0.60 | 0.27-1.33 | 0.204 | 0.57 | 0.21-1.53 | 0.267 |
| **Hypoxemia index** | | | | | | |
| Mild | reference | | | | | |
| Moderate | 1.14 | 0.54-2.40 | 0.725 | 1.08 | 0.39-3.04 | 0.879 |
| Severe | 0.50 | 0.15-1.68 | 0.264 | 0.50 | 0.08-3.10 | 0.457 |
| PEEP > 5cm $H_2O$ | 1.28 | 0.63-2.58 | 0.498 | 2.96 | 1.07-8.19 | 0.037 |
| Tidal volume>400ml | 0.99 | 0.48-2.04 | 0.972 | 1.08 | 0.40-2.89 | 0.883 |
| APACHE II score | 1.02 | 0.98-1.07 | 0.288 | 1.06 | 0.99-1.12 | 0.073 |
| SOFA score | 1.04 | 0.95-1.15 | 0.389 | 1.14 | 1.00-1.31 | 0.056 |

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; BMI, body mass index; FiO2, fraction of inspired oxygen; Hb, hemoglobin; HCO3, bicarbonate; HR, heart rate; ICU, intensive care unit; PEEP, positive end expiratory pressure; RR, respiratory rate; SOFA score, Sequential Organ Failure Assessment score

Table 4. univariate logistic regression model with odds ratio for 30 days mortality

| | Unmatched cohort | | |
|---|---|---|---|
| | ß-coefficient | 95% CI | P value |
| BMI | 0.02 | -0.16-0.20 | 0.829 |
| Cerebrovascular disease | -1.86 | -3.84-0.12 | 0.065 |
| Metastatic cancer | 1.31 | -0.55-3.16 | 0.167 |
| Immunosuppressed | 2.40 | 0.31-4.50 | 0.025 |
| HR at ICU admission | -0.02 | -0.06-0.01 | 0.193 |
| Hb | 0.26 | -0.14-0.65 | 0.204 |
| Lactic acid | 0.60 | 0.10-1.10 | 0.018 |
| FiO2 | -0.00 | -0.05-0.04 | 0.914 |
| Metformin use | -0.19 | -1.76-1.39 | 0.816 |

BMI, body mass index; FiO2, fraction of inspired oxygen; Hb, hemoglobin; HR, heart rate;

Table 5. The association of treatment with metformin and 30 days mortality using multivariable regression analysis (unmatched cohort)

| | Propensity score matched cohort | | |
|---|---|---|---|
| | ß-coefficient | 95% CI | P value |
| APACHE II score | 0.03 | -0.14-0.19 | 0.743 |
| SOFA score | 0.14 | -0.23-0.50 | 0.463 |
| BMI | 0.21 | -0.10-0.52 | 0.181 |
| Immunosuppressed | 2.63 | -1.06-6.31 | 0.162 |
| PEEP | 0.12 | -0.50-0.73 | 0.709 |
| HR | 0.02 | -0.05-0.09 | 0.603 |
| Hb | -0.03 | -0.90-0.84 | 0.942 |
| Lactic acid | -0.05 | -0.81-0.71 | 0.897 |
| LIS | 1.84 | -2.53-6.21 | 0.410 |
| Metformin use | 0.64 | -1.86-3.14 | 0.615 |

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; BMI, body mass index; Hb, hemoglobin; HR, heart rate; LIS, lung injury score; PEEP, positive end expiratory pressure; SOFA score, Sequential Organ Failure Assessment score

Table 6. The association of treatment with metformin and 30 days mortality using multivariable regression analysis (propensity score adjusted)

# DISCUSSION

This study provides some support for the hypothesis that preadmission metformin could have protective effect for ARDS in the clinic. We used propensity-matched analysis to overcome the weakness of our retrospective design. However, although pretreatment with metformin tends to lower the risk of mortality in ARDS patients, we found no significant difference in the outcome of ARDS between metformin users and nonusers in a propensity-matched analysis.

Among 558 patients who met the Berlin definition of ARDS and were subsequently diagnosed as having ARDS, 128 (23.3%) had diabetes. This finding was consistent with the previously reported decreased incidence of ARDS in diabetic patients.(5) Diabetes is regarded as protective factor for the development of ARDS even after adjustment for confounders, such as age and severity of illness.(3) It is thought that diabetes may be involved in pathogenesis of ARDS and alter the development by altering the immune system and inflammatory response, such as adherence of neutrophils to endothelium or bactericidal activity of inflammatory cells.(5, 6) Interestingly, whether serum concentration of glucose or HbA1c can influence the incidence of ARDS or not remains unclear.(1)

So far, metformin is not generally recommended for patients with chronic kidney, liver, or heart disease, and in patients with shock because of concern for lactic acidosis, which is a rare adverse effect. Our findings are consistent with this general idea.(22, 23) The number of patients with chronic kidney disease was much smaller for metformin users and was equal to propensity-matched analysis.

Contrary to our expectations for an anti-inflammatory effect of metformin that could influence the inflammatory process in ARDS, our findings of inflammatory markers including WBC, CRP, and lactic acid were that there was no significant distinction between metformin users and nonusers, but there was elevated CRP in metformin users in propensity-matched analysis.

Along the lines of our study, other investigators suggest that pretreatment with metformin attenuates ventilator-induced lung injury by preventing increased pulmonary microvascular permeability in response to deleterious mechanical ventilation in an animal model.(17) In a model of hyperoxia-induced experimental bronchopulmonary dysplasia, metformin showed a beneficial effect on survival and ameliorated pulmonary injury by reducing pulmonary inflammation and fibrosis.(24)

The pleiotropic properties of metformin, including anti-inflammation, antioxidant, endothelial barrier-enhancing, and antifibrotic effects,(14-16) might influence the progression of ARDS, especially in the early phase. However, because metformin is usually switched to insulin upon ICU admission, any protective effects of preadmission metformin use on ARDS are difficult to estimate. Previous studies showed a beneficial effect of metformin on decrease in inflammatory cytokines when added to intensive insulin therapy(18) and in mortality and morbidity of patients who underwent

cardiac surgery when taken before admission.(19) Unlike the hypoglycemic effect of metformin, little is known about the anti-inflammatory effect of metformin. No definite evidence from previous data, including precise pharmacokinetic aspects of metformin, was available to support the potential beneficial influence of metformin on the outcome of ARDS. Christiansen and colleagues(20) reported that the preadmission use of metformin was associated with a lower mortality in ICU. There are some explanations for these findings, such as that metformin exerts its anti-inflammatory action by increasing formation of the endogenous nucleoside adenosine, which could potently modulate inflammation.(25) However, unfortunately, there are virtually no data regarding the duration and persistence of anti-inflammatory properties of metformin; however, the glucose-lowering effect of metformin is known to be related to its half-life of under 5 hours.(26) Further studies are needed to identify the precise pharmacodynamics of the anti-inflammatory action of metformin.

We categorized our patients into two groups: metformin users, which included metformin monotherapy and combination therapy, and metformin nonusers. Potentially anti-inflammatory drugs has been proposed recently, such as peroxisome peroxidase agonists (PPARγ)(27), but only one patient was taking an anti-diabetic medicine combination of metformin and PPARγ. We performed propensity-matched analysis to compare the outcome of ARDS in diabetic patients regarding the effect of metformin. Even though we classified severity of ARDS into mild, moderate, and severe, pretreatment with metformin before admission did not show any remarkable beneficial effects on outcome.

There were significantly more patients who had chronic kidney disease among metformin nonusers, which is consistent with the strategy that metformin is seldom prescribed to patients with chronic kidney disease.(22, 23) However, metformin use did not significantly affect the outcome of ARDS, despite our adjustment for chronic kidney disease comorbidity (adjusted OR = 0.52, 95% CI 0.23 to 1.18, P = .117).

We evaluated the outcome of ARDS in terms of not only mortality alone, but also using various respiratory parameters including arterial blood gas analysis, ventilator demand, LIS, and lung compliance; however, none of these parameters showed any intergroup difference.

We acknowledge several limitations in this study. First, there was a small study population because of the single-center design. Only 33 ARDS patients with diabetes were prescribed metformin for glycemic control before ICU admission. Metformin is known to decrease food intake and body weight, and that may exert influence on the metabolic syndrome and is why metformin is initially recommended for obese diabetic patients.(28) However, body mass index (BMI) was 22.81 kg/m2 in metformin users and 22.10 kg/m2 in nonusers. Patients in our study were not considered obese according to the World Health Organization definition for obese Asians as having a BMI ≥25 kg/m2.(29) Second, because our study design was a retrospective cohort study, we could not estimate static lung compliance, and LIS was calculated using 3 components with the exception of lung compliance.(21) Inevitably, we

analyzed dynamic lung compliance instead of static lung compliance. Third, contrary to public expectations, there are few data about the anti-inflammatory pharmacokinetic action of metformin.

Although our study did not show any significant association between the anti-inflammatory effect of metformin or outcome of ARDS, few studies have examined diabetes and ARDS, especially metformin and ARDS.(17-20) Almost all previous data regarding the potential beneficial effect of metformin on lung injury were derived from an experimental model in animals. Further studies are needed to assess the influence of metformin on ARDS beyond its anti-diabetic effect.

# REFERENCES


1. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama. 2012;307(23):2526-33.
2. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. American journal of respiratory and critical care medicine. 2009;179(3):220-7.
3. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 1995;151(2 Pt 1):293-301.
4. Eisner MD, Thompson T, Hudson LD, Luce JM, Hayden D, Schoenfeld D, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2001;164(2):231-6.
5. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Critical care medicine. 2000;28(7):2187-92.
6. Iscimen R, Cartin-Ceba R, Yilmaz M, Khan H, Hubmayr RD, Afessa B, et al. Risk factors for the development of acute lung injury in patients with septic shock: an observational cohort study. Critical care medicine. 2008;36(5):1518-22.
7. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. The New England journal of medicine. 2001;345(19):1359-67.
8. Repine JE, Clawson CC, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetics. The Journal of infectious diseases. 1980;142(6):869-75.
9. Marhoffer W, Stein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes care. 1992;15(2):256-60.
10. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Critical care (London, England). 2009;13(1):R18.
11. Standards of medical care in diabetes--2013. Diabetes care. 2013;36 Suppl 1:S11-66.
12. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Annals of internal medicine. 2002;137(1):25-33.
13. Nyenwe EA, Jerkins TW, Umpierrez GE, Kitabchi AE. Management of type 2 diabetes: evolving strategies for the treatment of patients with type 2 diabetes. Metabolism: clinical and experimental. 2011;60(1):1-23.
14. Tsoyi K, Jang HJ, Nizamutdinova IT, Kim YM, Lee YS, Kim HJ, et

al. Metformin inhibits HMGB1 release in LPS-treated RAW 264.7 cells and increases survival rate of endotoxaemic mice. British journal of pharmacology. 2011;162(7):1498-508.
15. Grant PJ. Beneficial effects of metformin on haemostasis and vascular function in man. Diabetes & metabolism. 2003;29(4 Pt 2):6s44-52.
16. Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, et al. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. American journal of respiratory and critical care medicine. 2008;178(2):168-79.
17. Tsaknis G, Siempos, II, Kopterides P, Maniatis NA, Magkou C, Kardara M, et al. Metformin attenuates ventilator-induced lung injury. Critical care (London, England). 2012;16(4):R134.
18. Ansari G, Mojtahedzadeh M, Kajbaf F, Najafi A, Khajavi MR, Khalili H, et al. How does blood glucose control with metformin influence intensive insulin protocols? Evidence for involvement of oxidative stress and inflammatory cytokines. Advances in therapy. 2008;25(7):681-702.
19. Duncan AI, Koch CG, Xu M, Manlapaz M, Batdorf B, Pitas G, et al. Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery. Anesthesia and analgesia. 2007;104(1):42-50.
20. Christiansen C, Johansen M, Christensen S, O'Brien JM, Tonnesen E, Sorensen H. Preadmission metformin use and mortality among intensive care patients with diabetes: a cohort study. Critical care (London, England). 2013;17(5):R192.
21. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. The American review of respiratory disease. 1988;138(3):720-3.
22. Mahon J, Stiller C. The immunocompromised patient. Canadian Family Physician. 1987;33:349.
23. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. The Cochrane database of systematic reviews. 2006(1):Cd002967.
24. Chan NN, Brain HP, Feher MD. Metformin-associated lactic acidosis: a rare or very rare clinical entity? Diabetic medicine : a journal of the British Diabetic Association. 1999;16(4):273-81.
25. Chen X, Walther FJ, Sengers RM, Laghmani EH, Salam A, Folkerts G, et al. Metformin attenuates hyperoxia-induced lung injury in neonatal rats by reducing the inflammatory response. American journal of physiology Lung cellular and molecular physiology. 2015:ajplung.00389.2014.
26. Paiva M, Riksen NP, Davidson SM, Hausenloy DJ, Monteiro P, Goncalves L, et al. Metformin prevents myocardial reperfusion injury by activating the adenosine receptor. Journal of cardiovascular pharmacology. 2009;53(5):373-8.
27. Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, et al. Clinical pharmacokinetics of metformin. Clinical pharmacokinetics. 2011;50(2):81-98.
28. Mohanty P, Aljada A, Ghanim H, Hofmeyer D, Tripathy D, Syed T, et al. Evidence for a potent antiinflammatory effect of rosiglitazone. The

Journal of clinical endocrinology and metabolism. 2004;89(6):2728-35.
29. Pernicova I, Korbonits M. Metformin--mode of action and clinical implications for diabetes and cancer. Nature reviews Endocrinology. 2014;10(3):143-56.
30. World Health Organization; International Obesity Task Force. The Asian-Pacific Perspective: Redefining Obesity and Its Treatment. Geneva: WHO Western Pacific Region. 2000.

# 국문 초록

**서론:** 급성 호흡곤란 증후군은 높은 사망률을 보이지만, 저환기요법 외에는 입증된 치료법이 부족한 실정이고, 염증 반응 억제를 통한 치료법은 실패한 상황이다. 경구용 혈당강하제인 metformin 이 항염 작용이 있다고 보고되었으나 급성 호흡곤란 증후군의 예후에 미치는 영향은 알려져 있지 않아 이를 알아보고자 하였다.

**방법:**. 2005 년 1 월 1 일부터 2015 년 4 월 30 일까지 서울대학교병원 내과계중환자실에 입실한 급성 호흡곤란 증후군 환자 중 당뇨가 동반된 환자들을 후향적으로 분석하였다. 입원 전 3 개월 내 metformin 처방된 경우 metformin 사용군으로 정의되었다. Propensity score matching 후 30 일 사망률을 분석하였다.

**결과:** 당뇨가 동반된 급성 호흡곤란 증후군 환자 128 명들 중 metformin 사용군은 33 명이었다. Propensity score matching 후 30 일 사망률은 metformin 사용군에서 낮았으나 통계적 유의성은 없었다 (42.4 vs. 56.4%, P=0.265). Ventilator free days 와 ICU free days 도 양군간 차이는 없었다. 다변량 회귀분석에서 metformin 사용 여부는 30 일 사망률을 감소시키는 경향을 보였으나, 역시 통계적인 유의성은 없었다 (ß-coefficient -0.19, 95% CI -1.76-1.39, P=0.816).

**결론:** 중환자실 입실 이전 사용된 metformin 은 급성 호흡곤란 증후군 환자의 사망률을 감소시키는 경향을 보였으나 통계적으로 유의하지는 않았다. 향후 metformin 사용의 효과에 대해 더 많은 환자군을 통한 연구가 필요하겠다.

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**주요어 : 급성 호흡곤란 증후군; 당뇨병; metformin; 예후**

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