Evaluating the effect of Ondansetron on Reducing ICU Mortality in Patients with Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is an abrupt decline in glomerular filtration, which is attributed to various causes, and greatly increased the mortality of patients. The purpose of this study was to identify medications that provide potentially beneficial effects on decreasing mortality of AKI patients. This was a retrospective cohort study using electronic medical record data of AKI patients in intensive care unit (ICU) and the endpoint outcome was patient mortality in ICU. We evaluated the medical records from two ICU databases, MIMIC III and eICU, to find factors with potential effect on reducing ICU mortality. We used logistic regression to investigate associations between medications received and mortality in AKI patients from the MIMIC III database. Drugs associated with lower death rates were validated using the eICU database. We afterwards used acute physiology age chronic health evaluation (APACHE) predicted mortality for matching of the patient's baseline severity of illness with R package Match It function "matchit". A chi-square test to calculate the significance of drug use and mortality was followed. Several drugs showed potential beneficial effects on reducing mortality, and most were used for potentially fatal illnesses (e.g. antibiotics, cardiac medications). Ondansetron, not previously known as a life-saving drug, showed potential beneficial effect on reducing ICU mortality for AKI patients. This association was confirmed in a subsequent analysis using eICU database. Gene Expression Signature was used

to explore the molecular mechanism of the drugs on AKI. The therapeutic effect of ondansetron may be elicited through the modulation of NF-KB pathway and JAK-STAT pathway based on the analysis of gene expression signatures. In this study, we identified several drugs associated with lower mortality following AKI and discovered a potential novel indication for an antiemetic drug, ondansetron. Our findings provide real-world evidence to support clinical trials of ondansetron for AKI treatment.

Key words: Acute kidney injury; Ondansetron; Electronic Medical Records; ICU; Mortality

Abbreviation list: AKI: acute kidney injury; ICU: intensive care unit; ARF: acute renal failure; KDIGO: Kidney Disease: Improving Global Outcomes; NSAIDs: nonsteroidal anti-inflammatory drugs; GFR: glomerular filtration rate; CrCl: creatinine clearance; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration; SCr: serum creatinine level; RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; AKIN: Acute Kidney Injury Network; MIMIC III: Medical Information Mart for Intensive Care, version 3; APACHE IV: Acute Physiology Age Chronic Health Evaluation system predicted mortality version IV; DEG: differentially expressed gene; AUC: area under curve: SOFA Score: sequential organ failure assessment score; SAPSII: simplified acute physiology score II; NNT: number need to treat; SD: standard deviation; Bp: blood pressure; COPD: chronic obstructive pulmonary disease; SpO2: oxygen saturation; PaO2: partial pressure of oxygen; CO2: partial pressure of carbon dioxide; FiO2: fraction of inspired oxygen

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PREFACE

I sincerely appreciate my advisors Dr. Lirong Wang and Dr. Richard Bertz for their professional guidance and warm encouragement for my research during the last two years. Their instructions supported me a lot through my project. I have learned a lot from their abundant knowledge, and experience, as well as, their attitude towards study and life. I would also thank Dr. John Kellum and Dr. Sandra Kane-Gill for their valuable suggestions and powerful support of my project. Dr. Kirisci and Dr. Junmei Wang also provided me valuable suggestions about the thesis. I would like to thank my committee members for their help, every group meeting was very valuable in addressing project challenges. I would like to thank my committee members, Dr. Lirong Wang, Dr. Richard Bertz, Dr. Sandra Kane-Gill, Dr. Levent Kirisci and Dr. Junmei Wang.

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1.0 INTRODUCTION

1.1 ACUTE KIDNEY INJURY

Acute kidney injury (AKI), is an abrupt decline in glomerular filtration[1], which is attributed to various causes[2,3], is a common disorder and is encountered in various clinical settings[4,5]. Nearly 60% of patients worldwide will suffer from AKI during their intensive care unit (ICU) stay[6]. When AKI develops in the hospital, recognition is often delayed due to substandard biomarkers so supportive management is the only option[7]. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published the first interdisciplinary and international clinical practice guideline on AKI[4]. Recommendations were provided for supportive care, but no specific therapies were recommended Patients with AKI have poor short-term prognoses such as prolonged ICU and hospitalization stays and significantly reduced hospital survival. AKI results in a 1-year-mortality of 20-50% in critically ill patients[8]. Future development of chronic kidney disease, and risk for chronic dialysis and/or kidney transplantation are also known sequelae[9]. Unfortunately, the pathobiology of AKI is still unclear and no drugs have yet been approved for prevention or treatment of AKI[10].

1.1.1 SYMPTOMS OF ACUTE KIDNEY INJURY

The symptoms of AKI patients are regularly dominated by the various imbalanced kidney functions related to the disease. A severe life-threatening clinical presentation, abnormal heart rhythms, is caused by remarkably increased serum potassium level[11]. Vomiting, headache, nausea, and fatigue can come from the accumulation of nitrogen-containing substances in the body

circulation system[12]. The blood pressure can also be manipulated by the influenced fluid balance[13]. When the disease progresses, the fibrous tissue capsule surrounding the kidney can be stretched, clots appear in the blood vessels, and the kidneys become inflamed. In this situation, patients may feel pain on the side of body[12]. The AKI can also be caused by dehydration of the body. In that case, patients may feel thirsty and fluid depletion may appear on administrative examination[12].

1.1.2 CAUSES OF ACUTE KIDNEY INJURY

The causes of AKI are usually divided into three categories: prerenal, intrinsic and postrenal[14].Prerenal causes a decrease in the glomerular filtration rate (GFR) as the result of the decreased kidney blood/plasma flow. Low blood pressure, low blood volume (for example, dehydration), hepatorenal syndrome in the context of liver cirrhosis, cardiorenal syndrome caused by heart failure, renal artery stenosis, as well as renal vein thrombosis are considered as notable prerenal causes of AKI. In this situation, because one kidney is sufficient for normal body function, both kidneys have to be affected to trigger AKI symptoms[15].Intrinsic causes are also known as kidney causes, are subjects that can directly damage the kidney itself. Glomerulonephritis, rhabdomyolysis, acute interstitial nephritis, and tumor lysis syndrome[16] can be considered as a common cause in this category. Renal cells damaged by certain nephrotoxicity drugs are also considered as an intrinsic cause of AKI[15]. Postrenal causes are downstream diseases of the kidney that lead to acute renal injuries. Urinary tract obstruction caused by cancers of the prostate, ureters, bladder, obstructed urinary catheter, kidney stones, bladder stones, or benign prostatic hyperplasia is considered as the most frequent inducement of postrenal AKI[15]. As a consequence of several different causes, clinical history is helpful in the diagnosis of AKI.

1.1.3 DIAGNOSIS OF ACUTE KIDNEY INJURY

The diagnosis of AKI occurs when there is a rapid reduction in kidney function. It is based on clinical history, as well as, laboratory test information such as decreased creatinine clearance (CrCl), urine amount, or unusually increased, blood urea nitrogen (BUN), etc. Serum creatinine is an important measure for diagnosing AKI because it is an easily measured byproduct of muscle metabolism removed by glomerular filtration and also proximal tubular secretion[17]. As a consequence, serum creatinine concentration is used to calculate the CrCl which is roughly related to the estimated glomerular filtration (eGFR). The GFR is a clinically important feature of kidney function. Recently, the CrCl has been seen important in the case of severe kidney diseases nowadays because hypersecretion of creatinine by the proximal tubules occupies a larger fraction of the total creatinine cleared.

An explicit criterion for the diagnosis of AKI has been defined by KDIGO (the global nonprofit organization developing and implementing evidence-based clinical practice guidelines in kidney disease) in 2012[18]:

AKI can be diagnosed if any one of the following is present:

- Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which has occurred within the prior 7 days; or
- Urine volume < 0.5 ml/kg/h for 6 hours.

SCr: (serum creatinine level)

There are limitations to the criteria, for example, after kidney insult, it still takes at least one whole day for the serum creatinine concentration to rise. However, none of the new proposed alternative markers for kidney function have been considered as potent enough to take the place of creatinine[19]. A standard diagnostic definition of AKI has been provided by the RIFLE/AKIN criteria. The RIFLE criteria classify AKI patients into five classes: Risk, Injury, Failure, Complete kidney function loss and End-stage kidney disease base on the serum creatinine concentration and urine output. When the classification result is different based on the serum creatinine concentration and urine output, the worst classification will be used. The AKIN represents for the Acute Kidney Injury Network criteria, with a small modification on including small changes in serum creatinine (SCr) when occurs within 48h period[18]. After diagnosis and stage classification of AKI patients, further tests are normally required to ensure the causes of it. Renal ultrasound, bladder scan or post void residual can be conducted to rule out urinary retention.

1.1.4 TREATMENT AND PROGNOSIS OF ACUTE KIDNEY INJURY

Therapy for critically ill patients with AKI requires a focus on prevention with the coordination of a number of treatments across multiple disciplines[20]. The mitigation strategy should avoid using nephrotoxic substances, including iodinated contrasts (contrast medium CT), NSAIDs, as well as a number of nephrotoxic antibiotics, etc.[21]. In intensive care units (ICU), GFR and serum creatinine levels are often measured for measuring kidney function. Unfortunately, possibility of suffering from chronic kidney disease after and AKI episode is also highly possible. After AKI progression, 5-10% of patients will need a kidney transplant or life-long dialysis for they may not regain kidney function. Still there is a large proportion of patients with AKI die before discharge[22]. The mortality of AKI patients is considerably high, with 20% among all patients and this can even be as high as

50% for the patients in ICU. If the disorder is progressed after major abdominal surgery, the mortality is even over 12-fold increased[23]. AKI causes approximately 2 million deaths worldwide every year[8].

1.2 ONDANSETRON

Ondansetron is an antiemetic drug, which is used to prevent vomiting and nausea caused by surgery, cancer chemotherapy, or cancer radiation therapy[24]. Ondansetron works as a 5-HT_3 receptor antagonist, acting by preventing serotonin from binding with 5-HT_3 receptors located on adjacent vagal afferent nerves. This process can contribute to the inhibition of vagus nerve signaling, as well as the subsequent release of serotonin in the brainstem[25].

Ondansetron can be administrated through oral, rectal, thin-film, intramuscular or intravenous approaches[26]. Headache is the most common side effect of ondansetron, other common adverse effects are headache, itchiness, constipation, diarrhea and sleepiness. The adverse effects can be life-threatening when severe allergy or QT prolongation occurs[26]. It is also reported that ototoxicity can be observed when it is injected too fast[27]. Although, these more severe adverse effects are uncommon.

2.0 METHODS AND MATERIALS

2.1 RESEARCH OVERVIEW

A flow chart of our procedures is shown in **Figure 1**. We first identified patients with AKI from the MIMIC III database by using International Classification of Diseases, Ninth Revision (ICD9) codes. Clinical data were extracted (age, gender, first-day vital information, lab tests, comorbidities, medication use information and other variables to determine patients' conditions). Details of the data extraction can be found below. We used logistic regression to select variables that showed significant beneficial effects on ICU mortality. Among these variables, we identified drug(s) with potential beneficial effects and conducted literature searches to confirm the plausibility of each association. We then used data from a second independent database (eICU) to validate our findings, and we focused on drugs that were not expected to have a direct effect on survival from their primary use (e.g. drugs used to manage symptoms but not life-threatening conditions). Finally, we used gene signature analysis to find possible mechanisms for each drug candidate for their beneficial effects on AKI.

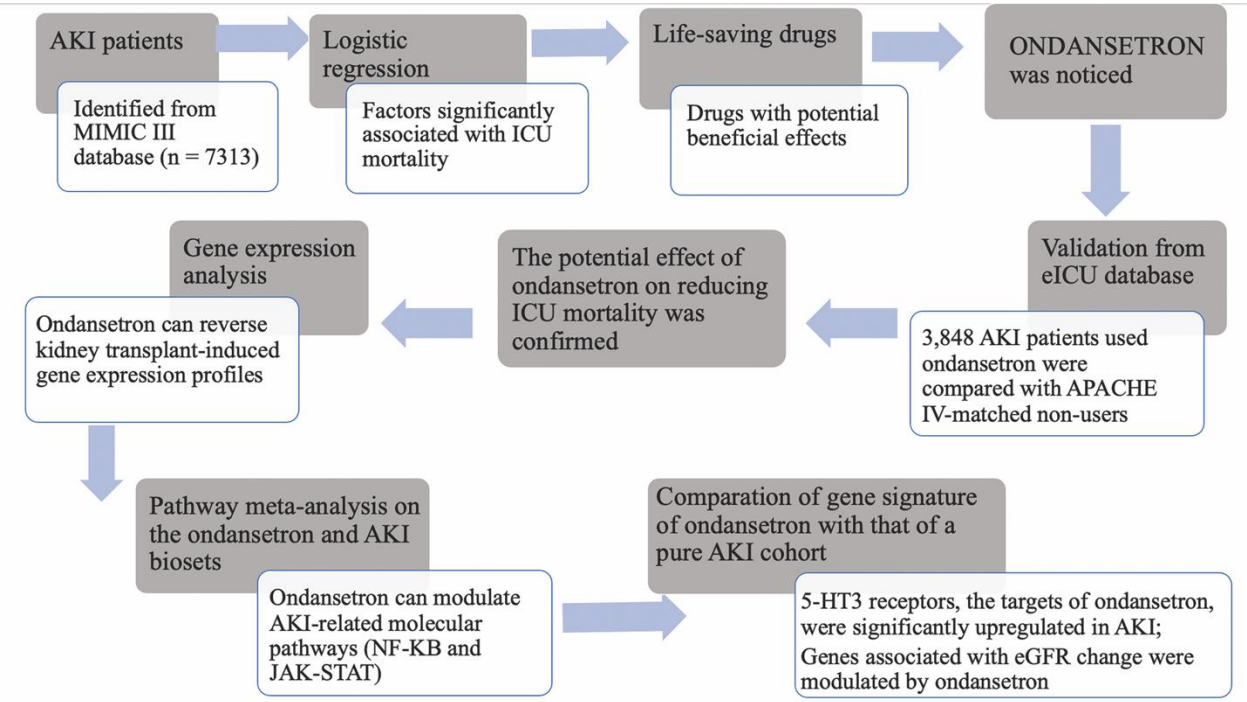

Figure 1. The flow chart of procedure. (AKI: Acute Kidney Injury; MIMIC III: Medical Information Mart for Intensive Care, version 3; ICU: Intensive Care Unit; APACHE IV: Acute Physiology Age Chronic Health Evaluation system predicted mortality version IV)

2.2 DATA SOURCE

Our discovery phase utilized data from the MIMIC III v1.4, which is the latest version of an publicly available clinical database developed by the MIT Lab for Computational Physiology[28]. This database comprises more than 60,000 ICU admissions to the Beth Israel Medical Center, Boston MA, from June 2001 to October 2012, including patient demographics, past medical history, laboratory tests, medication records, and diagnoses. To acquire access to MIMIC III, we completed the CITI "Data or Specimens Only Research" course (record ID: 36580723). ICD9-CM codes (**Supplementary Table 1)**, laboratory test results, medications and time events were extracted. The project was approved by the Institutional Review Boards of Beth Israel Deaconess

Medical Center and the Massachusetts Institute of Technology (Cambridge, MA). To guarantee privacy of patients, data were deidentified.

We used a second database, eICU, to validate our findings from the discovery phase[29]. The eICU database is a collaborative research database that consists of over 200,000 multi-center critical care records in ICUs in the United States through 2014-2015 and was made available by Philips Healthcare in partnership with the MIT Laboratory for Computational Physiology. The CITI "Data or Specimens Only Research" course was also required for access to this database. Data were deidentified to safeguard patient privacy.

We used the Illumina BaseSpace software to explore possible molecular mechanisms of drugs that have a potentially beneficial effect in AKI[30]. The BaseSpace software consists of a number of apps that provide next-generation sequencing, transcriptional, and proteomic data analysis mostly developed or optimized by Illumina.

2.3 POPULATION SELECTION CRITERIA

We used the ICD9-CM codes 584.5, 584.6, 584.7, 584.8 and 584.9 to search the diagnosis table in the MIMIC III database to identify patients with AKI. For eICU database, we used the keyword search ('acute renal failure') in the diagnosis table to identify patients with AKI. We also used ICD9-CM codes to verify the patients extracted from eICU.

2.4 DATA EXTRACTION

From the MIMIC III database, we extracted the demographic characteristics, physiological index, ICD9 codes, medications, laboratory tests, and vital status (alive or dead) upon ICU discharge. These variables were classified into three categories: first day vital information, medication use information, and other variables (**Supplementary Table 2**). The 50 most frequently used drugs in AKI patents in this database were filtered to be the medication use information. From the eICU database, we extracted acute physiology age chronic health evaluation (APACHE) system predicted mortality version IV[31], medications, and vital status on ICU discharge. We extracted drug and disease-induced differentially expressed genes (DEGs) by using the Illumina BaseSpace software. Missing values were found in physiological indexes such as average heart rate, average systolic blood pressure, average blood glucose and average albumin counts. All variable containing missing values were continuous variables, thus we filled the missing values with means of the whole column[32].

2.5 LOGISTIC REGRESSION TO IDENTIFY VARIABLES THAT SIGNIFICANTLY INFLUENCE ICU MORTALITY OF PATIENTS WITH AKI

We further analyzed the extracted data using multivariate logistic regression, in total 99 variables were considered and can be divided into three groups as suggested by Zimmerman, L. P., etc[33]: first-day vital and lab test information/comorbidities, medication use information and other variables. The first-day vital and lab test information/comorbidities contain creatinine level, temperature, hemoglobin concentration, etc. The medication use information were the 50 most frequently used drugs in AKI patents in MIMIC III database. The rest of the variables are the Sequential Organ Failure Assessment (SOFA) Score, the Simplified Acute Physiology Score

(SAPS) II, the Elixhauser's Comorbidity Index and the KDIGO stages in the first 48 hours. After calculated the estimate of association and p-value for each variable, variables with p value < 0.05 were filtered and listed in **Table 1**. Death within ICU admission was considered as the primary outcome. Eleven variables were dropped because of collinearity between covariates for logistic regression to prevent unstable estimates and inaccurate variances which affects confidence intervals and hypothesis tests. If the variance inflation factor (vif) was greater than 10, the variable will be dropped. The dropped variables include paralysis, hypothyroidism, peptic ulcer disease, obesity, weight loss, blood loss anemia, deficiency anemias, drug abuse, psychoses, cardiac arrhythmia, and depression.

2.6 VALIDATION OF OUR FINDINGS USING THE EICU DATABASE

We then validated our findings with the eICU database. We matched APACHE IV predicted mortality between patients who ever took a drug of interest with patients who did not to balance the baseline death propensity. Patients were matched one to one with the nearest APACHE IV score. If a patient has several matches from the other group, the corresponding patient will be chosen randomly. We then compared the ICU mortality rates for these two groups by chi-square test[34]. The APACHE IV predicted mortality was originally designed to predict the mortality risk[35]. Our assumption is that those matched patients will have similar death possibility. If a drug has beneficial effect on AKI, the death rate of the user group will be different from that of the non-user group. The number need to treat (NNT) was also calculated to represent the number of patients that need to be treated by the drug to express the significant beneficial effect.

2.7 INVESTIGATION OF POSSIBLE MOLECULAR MECHANISMS BY COMPARISON OF GENE TRANSCRIPTIONAL PROFILES

To understand the molecular mechanism behind the potential beneficial effects of a drug of interest on AKI mortality, we analyzed the gene expression profiles induced by drugs associated with lower ICU mortality in our analyses. DEGs induced by drugs were collected from Illumina BaseSpace software. In BaseSpace, only genes with p values <0.05 and absolute fold changes greater than 1.2 were considered as DEGs. All the DEGs induced by a drug can be considered as a gene signature for this drug. The drug-induced gene expression datasets were selected by searching with drug names. We then used the drug-induced DEGs to search against disease-induced DEGs (three biosets, named Kidney from transplant patient with toxic drug effects and UTI _vs_ normal kidney, Kidney from transplant patient with toxic drug effects _vs_ normal kidney and Kidney from transplant patient with toxic drug effects, UTI, and ARII_vs_ normal kidney, respectively) to find potential associations between these drugs and kidney diseases through the commonly modulated genes. The molecular pathways of those common genes involved were collected through meta-analysis function in BaseSpace to investigate possible molecular mechanisms for beneficial effects. All BaseSpace analyses were performed using the default parameters.

2.8 VALIDATION OF ONDANSETRON GENE SIGNATURE IN A HUMAN "PURE AKI" COHORT

To further elucidate the molecular mechanisms of ondansetron in AKI, we validated the gene signature of ondansetron in transcriptome data from a pure AKI cohort (GEO ID: GSE30718). Because some degree of AKI happens in all kidney transplantation patients, an excellent human AKI model can be found in early kidney transplants without rejection. In a prospective study of 234 kidney transplant biopsies for clinical indications, kidneys with rejection and kidney disease (other than AKI) by histologic criteria were excluded, and those with nondiagnostic suspicious histologic lesions were also excluded[36].

These criteria identified a "pure AKI" cohort of 28 biopsies with mean eGFR of 26 ml/min[36]. A total of 11 pristine protocol biopsies represented kidneys with a stable future function (at least 2 years of follow-up) after transplantation, no evidence for AKI or rejection by histology, and no clinical indication for biopsy (clinical or subclinical, before or after biopsy) were used as the controls in this study. The statistical comparison was obtained by estimated marginal means (also known as least-squares means) using R. Through orthology mapping, we were able to identify 1,333 gene expression alternations in the human AKI cohort. The DEGs were defined using a stringent threshold of 1.5-fold changes and a p value of less than 0.0001.

2.9 STATISTICAL ANALYSIS

The top 50 frequently used drug in AKI patients from MIMIC III database was filtered using Python, version 3.8.6 (Python Software Foundation, Wilmington, DE, USA). The logistic regression was performed in R, version 4.0.2 (The R Foundation for Statistical Computing, Vienna,

Austria), using caret package to measure the association between patient ICU mortality and variables. The variables with potential beneficial effect on reducing ICU mortality was reflected. The sensitivity was calculated by the formula (TP/TP + FN), the specificity was calculated by the formula (TN/TN + FP). TP, TN, FN, FP was true positive rate, true negative rate, false negative rate and false positive rate, respectively. Receiver operator characteristic (ROC) curve was plotted between TP (Y axis) and FP Rate (X Axis). The area under the curve (AUC) of ROC was therefore calculated. Among the medication use information, ondansetron was noticed because of the relatively high association with mortality and less association with life-saving effect. To validate the potential beneficial effect of ondansetron on reducing ICU mortality of AKI patients, the $\chi 2$ (chi-square) test was performed in eICU database to evaluate the difference of death rates between ondansetron users and non-users. To predict mortality of the patient of both groups, matching process to balance the baseline APACHE IV was conducted using R[37] package Match It[38] function "matchit" (method ="nearest", ratio =1, discard = "none", caliper = 0.05). Student t-test[39] was used to measure the mean difference of ICU mortality between the ondansetron users and non-users. All statistical t-tests were calculated by R. The NNT was calculated as the inverse of the absolute risk reduction (ARR) expressed as a decimal. The ARR was calculated by subtracting the rate of control events from the rate of experimental events, that is, the mortality rate of the two groups. The Running Fisher algorithm is used by Basespace software to assess the statistical significance of overlapping between two gene sets, where p-values are computed by a Fisher's exact test[40]. A $p < 0.05$ was used as the threshold for statistical significance for all analyses except where stated otherwise.

3.0 RESULTS

3.1 VARIABLES ASSOCIATED WITH ICU MORTALITY IN PATIENTS WITH AKI

From the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC III) database, we identified 9,536 patients with AKI, of whom 9,443 had completed information on demographics, ICU stay, and the first day vital information. We further excluded those patients with multiple ICU stays to simplify the calculation, resulting in 7,313 unique patients and 1,661 of those patients who died during their ICU stays (or ICU death rate: 22.7%). The basic characteristic of MIMIC3 patients can be found in **Supplementary Table 3.** The p-values are analyzed through Chi-Squared Test for categorical variables and t test for continuous variables. We used information from these 7,313 patients to build a logistic regression model and identified factors that contributed significantly to the prediction of ICU mortality (95% CI). **Table 1** lists variables with p values < 0.05. The sensitivity, specificity, and AUC (area under curve) of this logistic regression model are 0.93, 0.96 and 0.86 respectively.

Table 1. Estimate coefficients and significance of factors that influence ICU mortality of patients with AKI

Variables	**Estimate**	**Std. Error**	**Z Value**	**Pr(>|Z|)**
Warfarin	-1.485	0.177	-8.41	4.15E-17
Oxycodone	-1.070	0.137	-7.83	4.96E-15

Lisinopril	-0.857	0.200	-4.28	1.89E-05
Heparin	-0.651	0.104	-6.29	3.11E-10
Magnesium Sulfate	-0.560	0.101	-5.56	2.77E-08
Haloperidol	-0.553	0.125	-4.44	9.18E-06
Glucagon	-0.464	0.142	-3.28	0.00104
Metoprolol	-0.454	0.102	-4.44	9.11E-06
Ondansetron	-0.447	0.130	-3.45	0.000561
Furosemide	-0.359	0.101	-3.55	0.000384
Acetaminophen	-0.332	0.098	-3.40	0.000663
Hydralazine	-0.323	0.131	-2.46	0.0137
Hydromorphone	-0.299	0.132	-2.26	0.0238
Creatinine_Mean	-0.283	0.044	-6.50	8.22E-11
Docusate	-0.270	0.122	-2.22	0.0265
Hemoglobin_Mean	-0.252	0.088	-2.87	0.00408
Pantoprazole	-0.242	0.095	-2.55	0.0109
Tempc_Mean	-0.225	0.061	-3.71	0.000207
Spo2_Mean	-0.083	0.016	-5.30	1.19E-07
SOFA	-0.052	0.019	-2.67	0.00750

Diasbp_Mean	-0.041	0.009	-4.41	1.02E-05
Platelet_Mean	-0.001	0.0004	-3.61	0.000308
Bun_Mean	0.006	0.002	2.72	0.00655
Ptt_Mean	0.009	0.002	4.22	2.48E-05
Meanbp_Mean	0.040	0.012	3.48	0.000497
Resprate_Mean	0.042	0.010	4.20	2.72E-05
SAPSII	0.043	0.004	9.79	1.21E-22
F_Mean	0.088	0.030	2.92	0.00346
Bicarbonate_Mean	0.094	0.038	2.50	0.0123
Lactate_Mean	0.104	0.028	3.69	0.000221
Aniongap_Mean	0.151	0.038	3.96	7.54E-05
Midazolam	0.288	0.133	2.16	0.0307
Lorazepam	0.324	0.095	3.42	0.000625
Aki_Stage_48hr	0.341	0.066	5.15	2.63E-07
Meropenem	0.635	0.138	4.60	4.16E-06
Stroke	0.705	0.182	3.87	0.000110
Fentanyl	0.744	0.134	5.56	2.71E-08
Amiodarone	0.749	0.129	5.80	6.51E-09

Solid_Tumor	0.752	0.301	2.50	0.01229
Norepinephrine	1.233	0.115	10.76	5.09E-27
Morphine	1.735	0.094	18.54	9.88E-77

SOFA Score: Sequential Organ Failure Assessment Score

SAPSII: Simplified Acute Physiology Score (SAPS) II

KDIGO: Kidney Disease Improving Global Outcomes

Estimate coefficients show two sides of effect, positive and negative. A negative coefficient means that a factor is associated with increased survival vice versa. Death rates among patients with AKI with all the 50 drugs can be found in **Supplementary Table 4**.

3.2 DRUGS WITH POTENTIALLY BENEFICIAL EFFECTS ON AKI MORTALITY

We performed a literature search on all drugs identified to have effects of mortality (**Supplementary Table 5**). Nine of 15 drugs with negative coefficients in **Table 1** were reported to have a beneficial effect on decreasing ICU mortality. Among the 6 drugs (haloperidol, ondansetron, acetaminophen, hydromorphone, pantoprazole and lorazepam) not reported with having beneficial effect on decreasing ICU mortality, ondansetron stood out as an antiemetic, which seemed to be less related to preventing death and AKI recovery. Though indication bias may exist for these 6 drugs, ondansetron showed the best performance on decreasing ICU mortality in patients with AKI with the least connection of indication for 'life-saving' effect, which worth our further validation in the next step.

3.3 VALIDATION OF BENEFICIAL EFFECTS OF ONDANSETRON USING THE EICU DATABASE

We identified 12,676 patients with AKI from the eICU database. The mean values of APACHE IV predicted mortality from patients receiving/not receiving ondansetron were significantly different. After the matching procedure of a ratio of 1:1 matching (3,848:3,848 patients were matched), the APS scores between the two groups are nearly the same with a t-test p-value around 1. The detailed basic characteristics of eICU patients before matching can be found in **Supplementary table 6** and the basic characteristics after matching can be seen in **Supplementary table 7**. The p-values come from Chi-Squared Test for categorical variables and t test for continuous variables. Detailed information of the samples before and after matching is shown in **Supplementary Table 8**. **Supplementary Table 9** illustrates the detailed ICU death rates among 12,676 patients with AKI with top 50 used drugs in eICU database.

After the baseline APACHE IV predicted mortality adjustment, we saw a significantly lower ICU mortality (14.31%) in the ondansetron group than in the non-ondansetron matched control group (16.37%), P = 0.023; **Table 2**.

Table 2. The contingency table of the death event occurred in patients receiving/not receiving ondansetron. P-value is calculated with chi-square test.

	Non-Ondansetron	**Ondansetron**	**Total**	**P-value**
Death	548	479	1027	0.023

Alive	3300	3369	6669	
Total	3848	3848	7696	

Death rates among patients with AKI with the 50 most frequently used drugs identified from MIMIC III and eICU can be found in **Supplementary Tables 4 and 9**.

3.4 MOLECULAR MECHANISM STUDY BY GENE EXPRESSION SIGNATURES

We further analyzed the gene expression profiles induced by ondansetron and AKI. Through the Basespace database, we found one ondansetron dataset from the Chemical Effects in Biological Systems database[41], where intestines from rats were treated with ondansetron in vivo and assayed for expression. We selected the intestine of rats + ondansetron at 84mg-kg in water by oral gavage 0.25d vs. vehicle to mimic the acute effects of this drug. Searching with this gene expression signature (GES) data, we found three biosets[42] of AKI from transplant patients with toxic drug effects (AKI1, AKI2 and AKI3 in **Table 3**). They overlapped with ondansetron bioset (Ondansetron in **Table 3**) with p values of 4.0E-08, 9.8E-07 and 4.9E-06, respectively. Here UTI stands for urinary tract infection, and ARII stands for acute rejection type II. An example showed detailed comparison between ondansetron-induced gene expression profile and bioset of kidney from transplant patients with toxic drug effects can be found in **Figure 2**.

Table 3. Comparation of ondansetron-induced gene expression profiles with three AKI gene expression profiles

Biosets	Bioset Name	Genes	Overlap p value	Common Genes
Ondansetron	Intestine of rats + ONDANSETRON at 84mg-kg in water by oral gavage .25d _vs_ vehicle	1815	-	-
AKI1	Kidney from transplant patient with toxic drug effects and UTI _vs_ normal kidney	3289	4.0E-08	269
AKI2	Kidney from transplant patient with toxic drug effects _vs_ normal kidney	4417	9.8E-07	345
AKI3	Kidney from transplant patient with toxic drug effects, UTI, and ARII_vs_ normal kidney	4695	4.9E-06	345

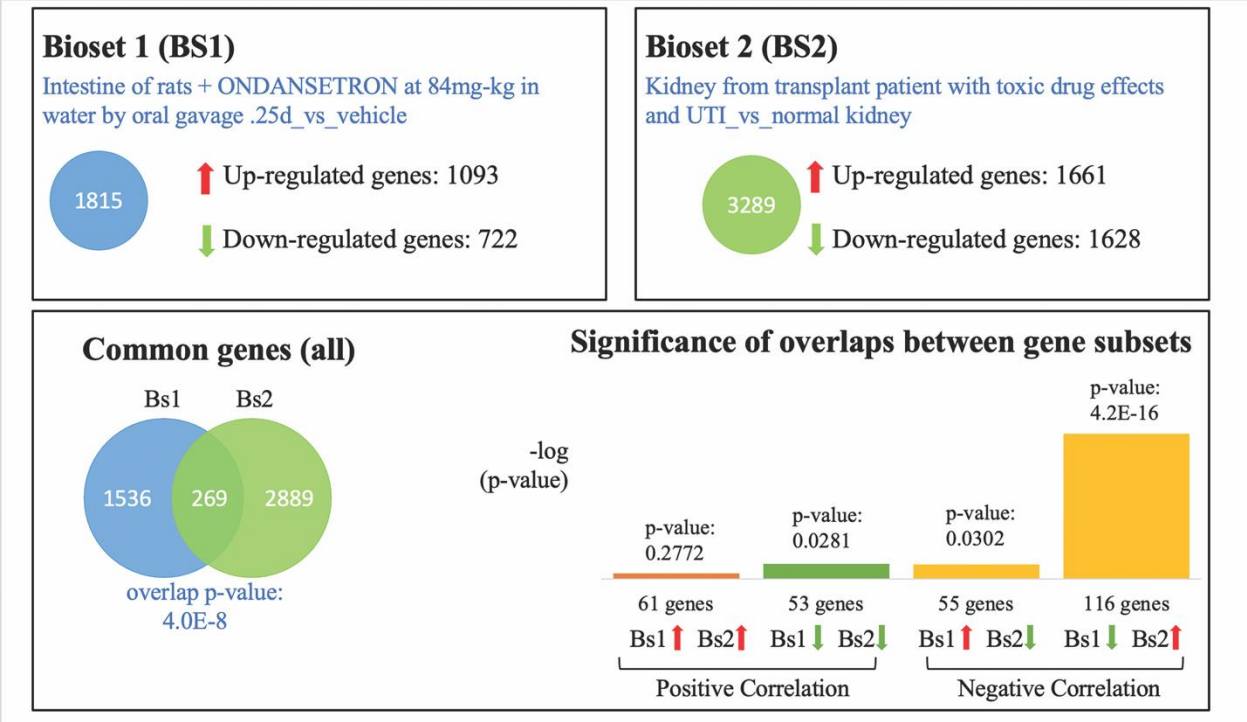

Figure 2. Detailed comparison between ondansetron-induced gene expression profile and kidney from transplant patient with toxic drug effects.

A detailed comparison of biosets named 'Intestine of rats + ONDANSETRON at 84mg-kg in water by oral gavage 0.25d _vs_ vehicle' and 'Kidney from transplant patient with toxic drug effects and UTI _vs_ normal kidney' is shown in **Figure 2**. We can see that ondansetron and AKI 1 have 1,815 and 3,289 DEGs, respectively, and they shared 269 common DEGs with significant p-values of 4.0E-8. Among those overlapping DEGs, 61 were both upregulated and 53 were both downregulated. A total of 55 genes were upregulated by ondansetron but were downregulated by AKI, while 116 genes were downregulated by ondansetron but were upregulated by AKI in AKI1 bioset.

To investigate the possible molecular mechanism of ondansetron on modulating AKI-related molecular pathways, we did a meta-analysis on these four biosets with the integrated function of BaseSpace. We found that pathways in cancer, microRNA target genes by miR381, miR200b, miR101, and miR26, were downregulated (**Supplementary Table 10**). Furthermore, miR381 was reported to play a role in rat models of renal ischemia reperfusion injury[43]. Target genes miR200b, miR101, and miR26 can be used as biomarkers for AKI[44,45]. As we can see from **Supplementary Table 11**, among the downregulated genes, Rela and Jak1 are the key proteins in the NF-KB pathway and JAK-STAT pathway, respectively. In comparison, these two genes are upregulated in AKI. Inhibitors for these two pathways have been reported to have beneficial effects for AKI[46,47].

3.5 VALIDATION OF ONDANSETRON GENE SIGNATURE IN THE TRANSCRIPTOME FROM A PURE AKI COHORT

Given that ondansetron is a 5-HT3 receptor antagonist, we examined the transcriptomes of 5-HT3 receptor genes (HTR3A, HTR3B and HTR3C). By neutralizing the ubiquitous minor changes inevitably induced by the kidney transplant process, the comparison of AKI kidneys to histologically pristine protocol biopsies of stable transplants will reveal the molecular features of AKI. In this transcriptome study, 5-HT3 receptor genes were all shown to be significantly upregulated (**Figure 3**). A volcano plot of the comparison results between the AKI and pristine protocol biopsy demonstrated significant positive and negative gene changes among the Ondansetron bioset. The volcano plot confirmed that JAK1, MAPK1, CTNNA1 and MET were upregulated in AKI by both fold change and P-values (**Figure 4**).

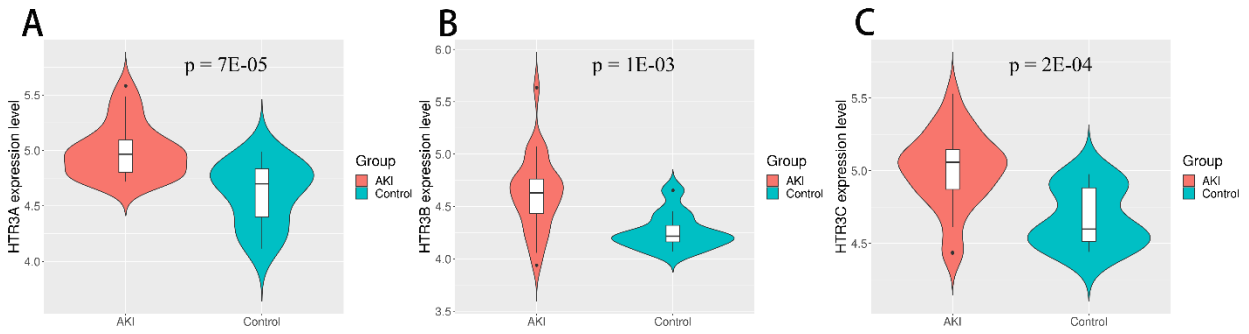

Figure 3. Changes of HT3 receptor genes (A for HTR3A, B for HTR3B and C for HTR3C) in patients with AKI compared with control (the pristine protocol biopsies).

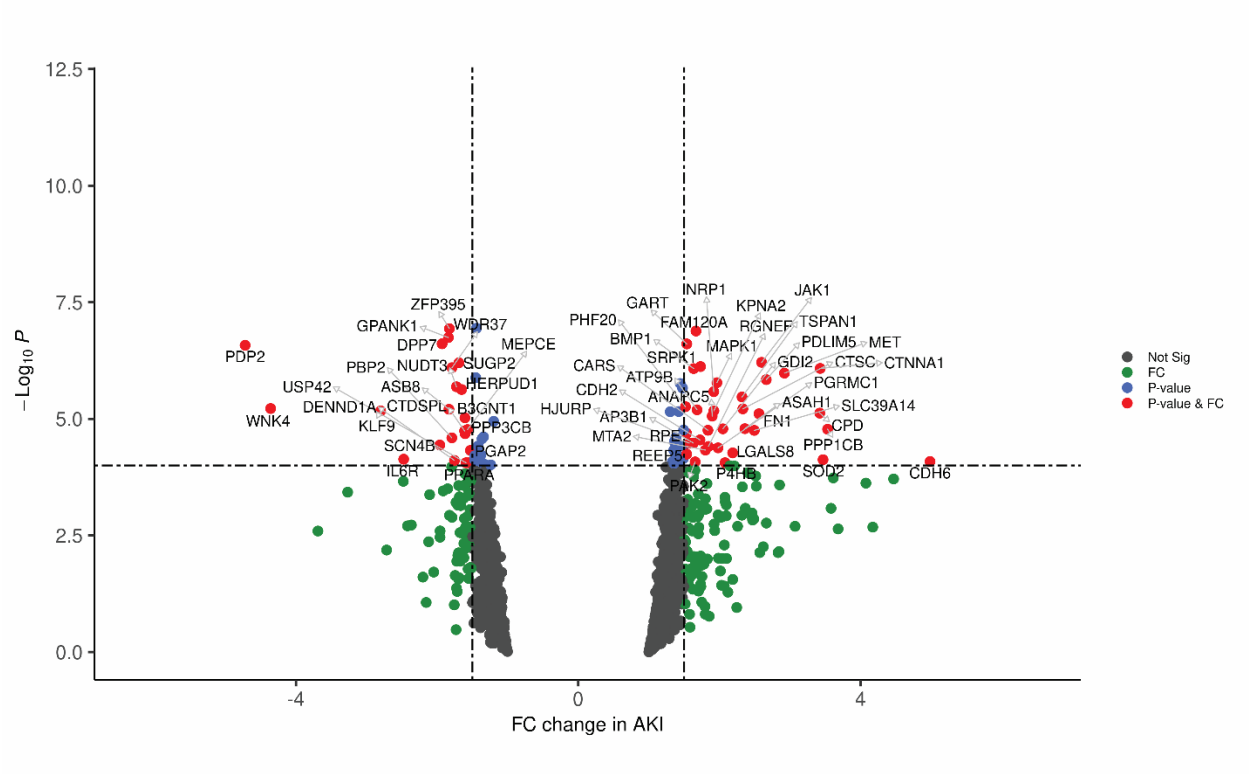

Figure 4. Volcano plot of gene expression changes of AKI compared with control.

Of note, Rela is not in the upregulated gene list because the fold change was 1.49, which is around the threshold. Conversely, FN1, which displayed little change in the other three biosets above, changed significantly. FN1 was reported to be associated with AKI by the comparative toxicogenomics database[48] with 499 references. Among the top 30 genes that were anticorrelating with eGFR at the time of biopsy in AKI biopsies, 8 genes were transcriptionally modulated by ondansetron. All 8 genes were upregulated in the human AKI cohort, and interestedly, we observed 6 out of 8 genes whose gene expression was downregulated by Ondansetron (**Table 4**).

Table 4. Genes whose expressions were negatively correlated with eGFR were also modulated by Ondansetron.

Gene Symbol	**Gene title**	**Correlation of gene mRNA expression with eGFR in human AKI cohort**	**Gene expression mRNA change in GSE30718 (AKI vs normal control)**		**Gene expression fold change by Ondansetron treatment**
			P value	Fold change	
KPNA2	Karyopherin a2 (RAG cohort 1, importin a1)	-0.72	6.73E-06	1.9	1.68
CASP1	Caspase 1, apoptosis-related cysteine peptidase (IL-1, b, convertase)	-0.72	1.00E-03	2.1	-8.03

TFPI	Tissue factor pathway inhibitor (lipoproteinassociated coagulation inhibitor)	-0.7	0.01	1.5	4.25
AMACR	a-methylacyl-CoA racemase	-0.68	2.80E-04	2.3	-2.38
GBP2	Guanylate binding protein 2, IFN-inducible	-0.67	1.00E-03	2.1	-4.71
MCL1	Myeloid cell leukemia sequence 1 (BCL2-related)	-0.66	3.90E-05	2.8	-3.07
MET	Met proto-oncogene (hepatocyte growth factor receptor)	-0.66	1.05E-06	2.9	-2.32
CPD	Carboxypeptidase D	-0.66	7.50E-06	3.4	-2.4

Finally, we examined genome-wide expression changes of all ondansetron pharmacological signature genes in this cohort. The number of differentially expressed genes (AKI vs control) was significantly enriched with a P value of 2.2E-11 (the supplementary table Ondansteron_geneSignature_inhumanAKIgenomicsdata.xlsx).

4.0 DISCUSSION

Most previous electronic medical record (EMR)-based studies have focused on nephrotoxic effects of medications[49-51]. There is limited prior literature that uses EMRs to repurpose Food and Drug Administration (FDA) approved drugs for AKI treatment. The development of new drugs is a costly endeavor with an average cost of $802 million[52], and the time for a new drug from preclinical compound to marketing can take up to 20 years[53]. Costs can be reduced to $40–$80 million through the repurposing discovery according to estimates, compared to the billions in costs to develop a new compound from an *in vitro* hit[54]. From a practical point of view, a drug identified from our study can be a potential treatment option for AKI patients with a validated safety profile since it has been safely used in AKI patients for other indications. However, more research is needed both to establish the efficacy of ondansetron for AKI treatment as well as to determine optimal dosing and duration of therapy.

To avoid confounders in the analysis of MIMIC III database, we dropped eleven variables because of collinearity between covariates to prevent unstable estimates and inaccurate variances which affects confidence intervals and hypothesis tests. The sensitivity, specificity, and AUC of this logistic regression model are 0.93, 0.96 and 0.86 respectively, indicating that the relationship between the variables and ICU mortality determined by this analysis is reliable. For the drugs identified to have potential effect on ICU mortality, several anesthetics showed opposite influences. One possible explanation for this is that different anesthetics were used in patients with different health conditions. The potential harmful effect on AKI patients of some anesthetic drugs may

because patients using these strong anesthetic drugs are in more severe condition in ICU, for example, patients requiring surgical operations, thus lead to higher mortality in this patient group. Among the drugs we found to be associated with reduced mortality in critically ill patients with AKI, ondansetron is of most interest for several reasons. First, it is an antiemetic drug that there are no reports or clinical trials to suggest its beneficial effect on decreasing mortality either in patients with AKI or other ICU patients. Second, ondansetron is a selective antagonist on the serotonin (5-HT3) receptor[55], which is a receptor with wide distribution in the human body[56] and its expression is upregulated in AKI (**Figure 3**). This might suggest that this receptor is a drug target in AKI.

There is a chance that the lower mortality in the ondansetron-treated group is the result of indication bias. Ondansetron is indicated for nausea which only awake, communicative patients can report. Patients in the ondansetron group thus may have lower disease severity. We controlled for this possibility by matching APACHE IV predicted mortality of ondansetron users with non-users and still found a significant, albeit smaller, impact on mortality in this matched analysis. However, in the analysis of eICU patients, the Number Need to Treat (NNT) was 56 [95% confidence interval 30.19 - 364.7]. This relatively high NNT may be due to the fact that patients were not prescribed ondansetron for treatment of AKI but for prevention/treatment of nausea and vomiting. These patients received comparably little dose in an irregular way. For example, when in the eICU database, there were 6,685 records of ondansetron use for 3,848 patients. Among these records, 5,849 (87.5%) were labeled as “prn” (as needed). For route of administration, 692 records were oral and 5,729 records were labeled as injections.

We further explored the possible molecular mechanisms by comparing gene expression signatures. Generally, if the genes regulated by the drug and the disease are in the opposite direction but show

a significant overlap, the drug may have a potential therapeutic effect on the disease. Our analysis revealed that there was a remarkable overlap of genes affected by both ondansetron and AKI. The most significant overlap occurred on the genes that are upregulated by AKI but downregulated by ondansetron. Furthermore, by validating the ondansetron gene signature in the "pure AKI" cohort, 5-HT3 receptor genes were significantly upregulated in patients with AKI. Hence the potential beneficial effect of ondansetron on AKI has support from molecular mechanisms.

There are limitations to this study. In our analysis, we adjusted for other medications and comorbidities to mitigate the effects of confounders in logistic regression, and we used matching to help alleviate the possible bias in baseline severity of illness in the validation step. However, we still cannot rule out the possibility of unknown confounder effects. In addition, ondansetron is approved in cancer patients and in the post-operative setting, implying the possibility of indication bias. However, a recent study examining drug combinations reported that ondansetron may increase the risk of AKI47. In patients receiving chemotherapy, GI symptoms may correlate with nephrotoxicity and thus it is difficult to say if an anti-emetic is a marker or mediator of AKI. In any case, these data do not support indication bias as an explanation for our findings. Finally, from gene expression data of molecular mechanism analysis, we have confidence that ondansetron has an effect on pathways relevant to AKI. As such, we believe that our results provide evidence that further study is warranted.

We identified a number of candidate drugs with apparent beneficial effects to reduce ICU mortality in patients with AKI Ondansetron, a drug that has never been reported before as a treatment for AKI, is proposed to be associated with improved survival following AKI in two independent databases. In addition, ondansetron can downregulate AKI-related genes and genes expressed through 5-HT3 receptor activation (and hence targeted by ondansetron) are

upregulated in patients with AKI. Our findings provide real-world evidence to support the need for clinical trials of ondansetron to treat AKI.

SUPPLEMENTAL APPENDIX

Supplementary Table 1. ICD9-CM codes for the extraction of patients with acute kidney injury from MIMIC III database

ICD9-CM Codes	**Corresponding Disease**
584.5	Acute kidney failure with lesion of tubular necrosis
584.6	Acute kidney failure with lesion of renal cortical necrosis
584.7	Acute kidney failure with lesion of renal medullary [papillary] necrosis
584.8	Acute kidney failure with other specified pathological lesion in kidney
584.9	Acute kidney failure, unspecified

Supplementary Table 2. Variables extracted from MIMIC III database for logistic regression

First-day Vital and lab test Information/comorbidities	**Medication Use Information**	**Other Variables**
Spo2_Mean	Morphine	SOFA
Tempc_Mean	Norepinephrine	SAPS-II
Resprate_Mean	Warfarin	Elixhauser's Comorbidity Index
Potassium_Mean	Magnesium Sulfate	KDIGO stages in the first 48 hours
Wbc_Mean	Fluconazole	
Pt_Mean	Furosemide	
Hematocrit_Mean	Oxycodone	
Creatinine_Mean	Haloperidol	
Hemoglobin_Mean	Heparin	
Platelet_Mean	Metoclopramide	
Peripheral_Vascular	Metoprolol	
Meanbp_Mean	Meropenem	
Ptt_Man	Lisinopril	
Lactate_Mean	Propofol	
Diasbp_Mean	Captopril	
Chloride_Mean	Amiodarone	

Sodium_Mean	Hydralazine	
Bicarbonate_Mean	Acetaminophen	
Albumin_Mean	Piperacillin	
Sysbp_Mean	Phytonadione	
Glucose_Mean	Lactulose	
Glucose_Mean	Ondansetron	
Pulmonary_Circulation	Nitroglycerin	
Bilirubin_Mean	Fentanyl	
Inr_Mean	Albuterol	
Heartrate_Mean	Ipratropium	
Aniongap_Mean	Bisacodyl	
Bun_Mean	Tacrolimus	
Bands_Mean	Prednisone	
Liver_Disease	Senna	
Metastatic_Cancer	Aspirin	
Stroke	Cefepime	
Chronic_Pulmonary	Hydromorphone	
Lymphoma	Insulin	
Alcohol_Abuse	Levofloxacin	
Rheumatoid_Arthritis	Metronidazole	
Renal_Failure	Lorazepam	
Hypertension	Famotidine	
Congestive_Heart_Failure	Midazolam	

Solid_Tumor	Chlorhexidine	
Coagulopathy	Dexamethasone	
Age	Diltiazem	
Gender	Glucagon	
	Pantoprazole	
	Docusate	
	Vancomycin	
	Atorvastatin	
	Levothyroxine	

SOFA Score: Sequential Organ Failure Assessment Score
SAPSII: Simplified Acute Physiology Score (SAPS) II
KDIGO: Kidney Disease Improving Global Outcomes

Supplementary Table 3. basic characteristic of MIMIC3 patients

(0 is for patients not administrated with ondansetron and 1 is for patients administrated with ondansetron)

	level	**0**	**1**	**p-value**
n		6142	1171	
Heart rate (mean (SD))		87.14 (17.14)	88.48 (17.57)	0.015
Systolic bp (mean (SD))		115.85 (17.64)	118.28 (18.15)	<0.001
Diastolic bp (mean (SD))		58.52 (11.12)	60.97 (11.93)	<0.001
Mean bp (mean (SD))		75.26 (11.43)	76.71 (12.14)	<0.001
Respiratory (mean (SD))		20.15 (4.43)	19.59 (4.14)	<0.001
Temperature (mean (SD))		36.72 (0.73)	36.76 (0.67)	0.08
SpO2 (mean (SD))		96.60 (3.43)	96.78 (2.59)	0.081
Glucose (mean (SD))		147.39 (52.77)	144.80 (49.19)	0.12
Congestive heart failure (%)	0	6125 (99.7)	1166 (99.6)	0.569
	1	17 (0.3)	5 (0.4)	
Pulmonary circulation (%)	0	6094 (99.2)	1159 (99.0)	0.504
	1	48 (0.8)	12 (1.0)	
Peripheral vascular (%)	0	5972 (97.2)	1149 (98.1)	0.1
	1	170 (2.8)	22 (1.9)	
Hypertension (%)	0	6140 (100.0)	1170 (99.9)	0.975
	1	2 (0.0)	1 (0.1)	
Age (mean (SD))		88.53 (68.73)	74.47 (53.16)	<0.001
Anion gap (mean (SD))		16.16 (4.25)	15.99 (4.03)	0.201
Albumin (mean (SD))		3.02 (0.50)	3.07 (0.51)	<0.001

Bicarbonate (mean (SD))		22.01 (5.10)	21.80 (4.84)	0.18
bilirubin (mean (SD))		2.46 (4.58)	2.50 (4.88)	0.789
Creatinine (mean (SD))		2.13 (1.69)	2.22 (1.99)	0.125
Glucose (mean (SD))		152.96 (67.01)	149.56 (64.42)	0.109
Hematocrit (mean (SD))		31.97 (5.59)	31.54 (5.63)	0.016
Hemoglobin (mean (SD))		10.67 (1.93)	10.53 (1.97)	0.024
Lactate (mean (SD))		2.87 (2.12)	2.60 (1.59)	<0.001
Platelet (mean (SD))		216.30 (120.48)	219.35 (120.68)	0.426
Potassium (mean (SD))		4.34 (0.66)	4.29 (0.68)	0.023
Sodium (mean (SD))		138.56 (5.80)	137.61 (4.82)	<0.001
Bun (mean (SD))		43.20 (27.71)	40.40 (28.36)	0.002
White blood cell (mean (SD))		13.19 (11.07)	12.73 (9.94)	0.19
Stroke (%)	0	5864 (95.5)	1124 (96.0)	0.482
	1	278 (4.5)	47 (4.0)	
GENDER (%)	0	2597 (42.3)	569 (48.6)	<0.001
	1	3545 (57.7)	602 (51.4)	

SD: Standard Deviation
Bp: Blood pressure
COPD: Chronic obstructive pulmonary disease
SpO2: Oxygen saturation
BUN: Blood Urea Nitrogen
PaO2: Partial Pressure of Oxygen
CO2: partial pressure of carbon dioxide
FiO2: Fraction of inspired oxygen

Supplementary Table 4. Detailed Intensive Care Unit death rates among 7313 patients with Acute Kidney Injury with top 50 used drugs in MIMIC III database

Drug name	**Death_rate**
Lisinopril	0.05310881
Warfarin	0.06730769
Oxycodone	0.09497965
Captopril	0.13303769
Ondansetron	0.14090521
Tacrolimus	0.15328467
Hydralazine	0.15511811
Atorvastatin	0.1560575
Hydromorphone	0.16617503
Metoprolol	0.16998792
Glucagon	0.17604356
Docusate	0.17857143
Aspirin	0.17896679
Acetaminophen	0.1812596
Prednisone	0.19130435
Nitroglycerin	0.19241706
Bisacodyl	0.19445953
Haloperidol	0.19484536

Magnesium Sulfate	0.2033577
Heparin	0.21041168
Furosemide	0.21463681
Levothyroxine	0.21839081
Insulin	0.24112242
Metoclopramide	0.24866596
Pantoprazole	0.25445605
Albuterol	0.2571977
Ipratropium	0.25886688
Famotidine	0.26079295
Levofloxacin	0.27020358
Diltiazem	0.27496382
Lorazepam	0.2855914
Propofol	0.28782288
Vancomycin	0.30002768
Lactulose	0.32634731
Chlorhexidine	0.32848233
Fluconazole	0.33333333
Piperacillin	0.3369631
Metronidazole	0.33804548
Amiodarone	0.33894737
Cefepime	0.34080718

Phytonadione	0.36416667
Dexamethasone	0.375
Morphine	0.37647878
Fentanyl	0.3778672
Midazolam	0.38999514
Meropenem	0.4605042
Norepinephrine	0.49751244
All	0.22712977

Supplementary Table 5. Detailed information of medications identified with significant effects on Intensive Care Unit mortality for Patients with Acute Kidney Injury (Y, yes with clinical trials and/or literature supports; N, no report)

Medication	**Reducing ICU mortality of Patients with AKI by logistic regression analysis**	**Reported protective effect in all ICU patients**	**Reported protective effect for Patients with AKI in ICU**	**Medical use of drug**
Warfarin	Y	Y[57]	N	treat and prevent blood clots
Oxycodone	Y	Y[58]	N	treat moderate to severe pain
Lisinopril	Y	Y[59]	Y[60]	ACE inhibitor, can treat high blood pressure and heart failure.
Heparin	Y	Y[61]	N	anticoagulant, also used to treat heart attacks and unstable angina

Magnesium Sulfate	Y	Y[62]	Y[63]	prevention and control of seizures in preeclampsia and eclampsia
Haloperidol	Y	N	N	antipsychotic[64]
Glucagon	Y	Y[65]	N	treat severe low blood sugar
Metoprolol	Y	Y[66]	N	beta blocker
Ondansetron	Y	N	N	prevent nausea and vomiting[67]
Furosemide	Y	Y[68]	Y[69]	treat fluid retention (edema) and swelling
Acetaminophen	Y	N	N	analgesic[70]
Hydralazine	Y	Y[71]	Y[72]	treat high blood pressure
Hydromorphone	Y	N	N	treat moderate to severe pain[73]
Docusate	Y	N	N	treat constipation[74]
Pantoprazole	Y	N	N	treatment of stomach ulcers, erosive esophagitis due to gastroesophageal reflux disease (GERD)[75]
Midazolam	N	Y[76]	N	used for anesthesia, procedural sedation, trouble sleeping, and severe agitation

Lorazepam	N	N	N	treat anxiety disorders, trouble sleeping, active seizures, and chemotherapy-induced nausea and vomiting[77]
Meropenem	N	Y[78]	N	Antibiotics
Fentanyl	N	Y[79]	N	narcotic, treat severe pain
Amiodarone	N	N	N	treat heart rhythm problems[80]
Norepinephrine	N	Y[81]	N	treat low blood pressure and heart failure
Morphine	N	Y[57]	N	treat moderate to severe pain

Supplementary Table 6. The detailed basic characteristics of eICU patients before matching (0 is for patients not administrated with ondansetron and 1 is for patients administrated with ondansetron)

	level	**0**	**1**	**p-value**
n		8828	3848	
Gender (%)	Female	3852 (43.6)	1737 (45.1)	0.347
	Male	4974 (56.3)	2111 (54.9)	
	Unknown	2 (0.0)	0 (0.0)	
Age (%)	<=49	1632 (18.5)	771 (20.0)	<0.001
	>49	1474 (16.7)	723 (18.8)	
	>59	1994 (22.6)	868 (22.6)	
	>69	2046 (23.2)	876 (22.8)	
	>79	1682 (19.1)	610 (15.9)	
APACHE IV predicted mortality (mean (SD))		0.17 (0.22)	0.13(0.18)	<0.001
Congestive heart failure (%)	0	7398 (83.8)	3332 (86.6)	<0.001
	1	1430 (16.2)	516 (13.4)	
Cardiac arrhythmias (%)	0	6680 (75.7)	2973 (77.3)	0.056
	1	2148 (24.3)	875 (22.7)	
Hypertension (%)	0	7217 (81.8)	3153 (81.9)	0.821
	1	1611 (18.2)	695 (18.1)	
Coagulopathy (%)	0	8193 (92.8)	3620 (94.1)	0.01
	1	635 (7.2)	228 (5.9)	
Diabetes (%)	0	6976 (79.0)	3194 (83.0)	<0.001
	1	1852 (21.0)	654 (17.0)	
Liver disease (%)	0	7994 (90.6)	3502 (91.0)	0.436
	1	834 (9.4)	346 (9.0)	
COPD (%)	0	7857 (89.0)	3521 (91.5)	<0.001
	1	971 (11.0)	327 (8.5)	
Tumor (%)	0	8388 (95.0)	3621 (94.1)	0.038
	1	440 (5.0)	227 (5.9)	
Pulmonary circulation (%)	0	8539 (96.7)	3741 (97.2)	0.158
	1	289 (3.3)	107 (2.8)	
Respiratory failure (%)	0	5061 (57.3)	2461 (64.0)	<0.001
	1	3767 (42.7)	1387 (36.0)	
Temperature (mean (SD))		36.30 (1.26)	36.32 (1.15)	0.282

Respiratory rate (mean (SD))		26.78 (14.35)	27.76 (15.05)	0.001
Sodium (mean (SD))		138.15 (7.22)	136.97 (6.73)	<0.001
Heart rate (mean (SD))		105.02 (31.57)	105.20 (31.30)	0.768
Mean bp (mean (SD))		81.32 (44.62)	82.73 (44.88)	0.101
Blood pH (mean (SD))		7.31 (0.12)	7.33 (0.11)	<0.001
Hematocrit (mean (SD))		31.28 (7.12)	31.12 (7.13)	0.27
Creatinine (mean (SD))		2.79 (2.26)	2.96 (2.57)	<0.001
Albumin (mean (SD))		2.65 (0.67)	2.75 (0.67)	<0.001
PaO2 (mean (SD))		122.90 (84.67)	124.59 (82.57)	0.535
PCO2 (mean (SD))		41.47 (13.72)	40.23 (12.83)	0.005
Bun (mean (SD))		49.29 (31.00)	48.73 (32.43)	0.379
Glucose (mean (SD))		182.72 (132.14)	182.95 (135.72)	0.932
Bilirubin (mean (SD))		1.75 (3.80)	1.70 (3.33)	0.612
FiO2 (mean (SD))		64.85 (28.03)	62.65 (28.21)	0.016

SD: Standard Deviation
Bp: Blood pressure
COPD: Chronic obstructive pulmonary disease
SpO2: Oxygen saturation
BUN: Blood Urea Nitrogen
PaO2: Partial Pressure of Oxygen
CO2: partial pressure of carbon dioxide
FiO2: Fraction of inspired oxygen

Supplementary Table 7. The detailed basic characteristics of eICU patients after matching

	level	0	1	p
N		3848	3848	
Gender (%)	Female	1688 (43.9)	1737 (45.1)	0.345
	Male	2160 (56.1)	2111 (54.9)	
	Unknown	2(0.0)	0 (0.0)	
Age (%)	<=49	696 (18.1)	771 (20.0)	0.002
	>49	667 (17.3)	723 (18.8)	
	>59	854 (22.2)	868 (22.6)	
	>69	904 (23.5)	876 (22.8)	
	>79	727 (18.9)	610 (15.9)	
Predicted ICU mortality IV (mean (SD))		0.13 (0.18)	0.13 (0.18)	0.813
Congestive heart failure (%)	0	3222 (83.7)	3332 (86.6)	<0.001
	1	626 (16.3)	516 (13.4)	
Cardiac arrhythmias (%)	0	2951 (76.7)	2973 (77.3)	0.057
	1	897 (23.3)	875 (22.7)	
Hypertension (%)	0	3145 (81.7)	3153 (81.9)	0.836
	1	703 (18.3)	695 (18.1)	
Hypothyroidism (%)	0	3661 (95.1)	3707 (96.3)	0.011
	1	187 (4.9)	141 (3.7)	
Coagulopathy (%)	0	3592 (93.3)	3620 (94.1)	0.205
	1	256 (6.7)	228 (5.9)	
Diabetes (%)	0	3046 (79.2)	3194 (83.0)	<0.001
	1	802 (20.8)	654 (17.0)	
Liver disease (%)	0	3500 (91.0)	3502 (91.0)	0.968
	1	348 (9.0)	346 (9.0)	
COPD (%)	0	3411 (88.6)	3521 (91.5)	<0.001
	1	437 (11.4)	327 (8.5)	
Tumor (%)	0	3648 (94.8)	3621 (94.1)	0.011
	1	200 (5.2)	227 (5.9)	
Pulmonary circulation (%)	0	3720 (96.7)	3741 (97.2)	0.195
	1	128 (3.3)	107 (2.8)	
Respiratory failure (%)	0	2315 (60.2)	2461 (64.0)	0.001
	1	1533 (39.8)	1387 (36.0)	
Temperature (mean (SD))		36.35 (1.11)	36.32 (1.15)	0.231
Respiratory rate (mean (SD))		26.68 (14.39)	27.76 (15.05)	0.001
Sodium (mean (SD))		138.01 (7.03)	136.97 (6.73)	<0.001

Heartrate (mean (SD))		104.38 (31.63)	105.20 (31.30)	0.248
Mean bp (mean (SD))		82.12 (44.49)	82.73 (44.88)	0.546
Blood pH (mean (SD))		7.32 (0.12)	7.33 (0.11)	0.016
Hematocrit (mean (SD))		31.38 (6.94)	31.12 (7.13)	0.136
Creatinine (mean (SD))		2.76 (2.25)	2.96 (2.57)	<0.001
Albumin (mean (SD))		2.67 (0.65)	2.75 (0.67)	<0.001
PaO2 (mean (SD))		123.30 (87.77)	124.59 (82.57)	0.705
PCO2 (mean (SD))		41.41 (13.77)	40.23 (12.83)	0.027
Bun (mean (SD))		48.88 (30.58)	48.73 (32.43)	0.85
Glucose (mean (SD))		181.12 (132.40)	182.95 (135.72)	0.559
Bilirubin (mean (SD))		1.60 (3.29)	1.70 (3.33)	0.343
FiO2 (mean (SD))		62.80 (27.92)	62.65 (28.21)	0.895

SD: Standard Deviation
Bp: Blood pressure
COPD: Chronic obstructive pulmonary disease
SpO2: Oxygen saturation
BUN: Blood Urea Nitrogen
PaO2: Partial Pressure of Oxygen
CO2: partial pressure of carbon dioxide
FiO2: Fraction of inspired oxygen

Supplementary Table 8. The comparison of APACHE IV predicted mortality among patients receiving/not receiving ondansetron before and after matching.

	Non-Ondansetron		Ondansetron		P-value
	APACHE IV predicted mortality (mean (SD))	N	APACHE IV predicted mortality (mean (SD))	N	
Before matching	0.17 (0.22)	8828	0.13 (0.18)	3848	<0.001
After matching	0.13 (0.18)	3848	0.13 (0.18)	3848	0.999

Supplementary Table 9. Detailed Intensive Care Unit death rates among 12,676 patients with Acute Kidney Injury with top 50 used drugs in eICU database

Drug name	**Death rate**
Acetaminophen	0.12346723
Albuterol	0.1745897
Amiodarone	0.26989247
Aspirin	0.12632042
Atorvastatin	0.08865586
Bisacodyl	0.15659008
Captopril	Not used
Cefepime	0.22851153
Chlorhexidine	0.22298137
Dexamethasone	0.05813953
Diltiazem	0.12173913
Docusate	0.13647541
Famotidine	0.1844166
Fentanyl	0.23959778
Fluconazole	Not used
Furosemide	0.12086514
Glucagon	0.12974162
Hydromorphone	0.14119923

Haloperidol	0.20122888
Heparin	0.14303119
Hydralazine	0.08059701
Insulin	0.17200571
Ipratropium	0.17283465
Lactulose	0.23356009
Levofloxacin	0.14684466
Levothyroxine	0.10902256
Lisinopril	0.02170767
Lorazepam	0.22892041
Magnesium Sulfate	0.1721435
Meropenem	0.26996198
Metronidazole	0.23011844
Metoclopramide	0.15832206
Metoprolol	0.10787402
Midazolam	0.27306968
Morphine	0.23481414
Nitroglycerin	0.0758547
Norepinephrine	0.33662217
Ondansetron	**0.12487335**
Oxycodone	0.05555556
Pantoprazole	0.15181661

Phytonadione	0.33532934
Piperacillin	0.20039101
Prednisone	0.06049383
Propofol	0.26144658
Senna	0.2
Tacrolimus	0.04
Vancomycin	0.22929046
Warfarin	0.03533569
All	0.15266528

Supplementary Table 10. Enriched pathways in the Ondansetron and Acute Kidney Injury biosets

Pathways	**Genes**	**Ondansetron**	**AKI1**	**AKI2**	**AKI3**
Pathways in cancer	311	32(2.1E-17)	66(5.6E-30)	89(5.8E-40)	82(5.7E-36)
Predicted Gene Targets for miR-381	472	42(4.3E-20)	83(2.2E-30)	103(1.9E-34)	87(6.2E-26)
Predicted Gene Targets for miR-200b	428	34(6.8E-15)	75(2.9E-27)	101(1.1E-36)	86(1.7E-28)
Positive regulation of cell differentiation	482	39(2.7E-17)	67(7.8E-21)	89(4.2E-28)	92(4.7E-31)
Predicted Gene Targets for miR-101	386	24(1.7E-8)	69(3.0E-26)	94(5.0E-36)	75(8.3E-24)
Kinase binding	426	41(3.7E-21)	56(4.7E-18)	77(7.7E-26)	79(2.7E-28)
Targets of MicroRNA CAGTATT,MIR-200B,MIR-200C,MIR-429	448	32(1.1E-12)	77(4.1E-27)	93(1.4E-29)	80(1.3E-23)
Predicted Gene Targets for miR-26	448	36(8.6E-16)	71(1.5E-23)	93(3.1E-29)	83(3.2E-24)
Response to peptide hormone stimulus	326	31(5.6E-17)	59(5.1E-22)	86(5.2E-33)	65(2.0E-20)
Genes involved in Hemostasis	420	42(4.3E-21)	73(3.6E-26)	80(1.5E-22)	77(1.5E-21)

Supplementary Table 11. Detailed gene expression fold changes in Ondansetron and Acute Kidney Injury biosets

Gene	Ondansetron	AKI1	AKI2	AKI3
Rela	-265	1.37	-	1.64
Jak1	-10.7	1.74	0.65	0.36
Ctbp2	-10.3	-	-	-
Fn1	-10.3	-	-	-
Rb1	-9.02	-	1.51	1.48
Ctnnb1	-6.88	-2.1	-2.1	-2.42
Pld1	-5.95	-	1.52	1.67
Mapk9	-5.48	1.29	-1.8	-
Pten	-4.92	1.86	1.67	0.03
Casp3	-4.18	1.44	-1.53	-1.93
Mapk1	-4.09	2.94	1.88	1.89
Lamb2	-4.03	-	-	-
Tgfa	-3.86	-1.47	1.49	-
Cdkn2b	-3.79	-	-	-
Pik3r1	-3.77	1.91	-	-
Prkcb	-3.73	0.62	-0.31	-0.49
Itgb1	-3.18	-	-	-
Ctnna1	-2.95	1.63	2.1	1.96
Birc2	-2.85	-	-	-
Crk	-2.78	-	-	-
Kras	-2.58	1.86	1.61	-
Smo	-2.45	-	-	1.23
Met	-2.32	-	1.81	1.94
Msh2	-2.29	-	-	-
Erbb2	-2.24	-	1.64	1.73

Cycs	-2.08	1.78	-	-
Mapk3	-1.98	-	-	-
Tpr	-1.93	1.81	0.29	1.64
Mtor	-1.75	1.33	-	-
Cdc42	-1.7	-2.25	-1.91	-2.21
Plcg2	-1.63	1.98	-1.41	-1.46
Tgfb1	-1.54	-2.17	-1.37	-1.44
Mecom	1.46	2.08	-	1.76
Pdgfrb	1.49	-	-	1.65
Raf1	1.51	-0.08	-0.03	-0.12
Hdac1	1.52	-	-	-
Tgfb3	1.83	-	-	-
Axin2	2.12	-	-	-
Gsk3b	2.3	-	1.46	1.87
Sos2	2.47	-1.39	-	-

‘-’: means that the gene expression is within the fold change range of -1.2 to 1.2.

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