Cluster analysis driven by unsupervised latent feature learning of intensive care unit medications to identify novel pharmaco-phenotypes of critically ill patients

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Abstract

Unsupervised clustering of intensive care unit (ICU) medications may identify unique medication clusters (i.e., pharmacophenotypes) in critically ill adults. We performed an unsupervised analysis with Restricted Boltzmann Machine of 991 medications profiles of patients managed in the ICU to explore pharmacophenotypes that correlated with ICU complications (e.g., mechanical ventilation) and patient-centered outcomes (e.g., length of stay, mortality). Six unique pharmacophenotypes were observed, with unique medication profiles and clinically relevant differences in ICU complications and patient-centered outcomes. While pharmacophenotypes 2 and 4 had no statistically significant difference in ICU length of stay, duration of mechanical ventilation, or duration of vasopressor use, their mortality differed significantly (9.0% vs. 21.9%, $p < 0.0001$). Pharmacophenotype 4 had a mortality rate of 21.9%, compared with the rest of the pharmacophenotypes ranging from 2.5-9%. Phenotyping approaches have shown promise in classifying the heterogenous syndromes of critical illness to predict treatment response and guide clinical decision support systems but have never included comprehensive medication information. This first-ever machine learning approach revealed differences among empirically-derived subgroups of ICU patients that are not typically revealed by traditional classifiers. Identification of pharmacophenotypes may enable enhanced decision making to optimize treatment decisions.

Introduction

Medication regimens of critically ill patients in the intensive care unit (ICU) are complex and heterogeneous. [1,2] This heterogeneity of medication regimens has parallels to the common and lethal disease states of critical illness including sepsis and acute respiratory distress syndrome (ARDS). [3,4] Managing the heterogeneity of critical illness is a nearly universally cited challenge for ICU clinicians and researchers. [5,6] Phenotyping has been proposed to identify patterns of diagnosis and treatment response among these complex heterogenous syndromes. [7-9] In particular, phenotyping via artificial intelligence (AI) and machine learning (ML) has demonstrated potential to be a powerful methodology to handle Big Data generated by critically ill patients for identification of novel patient subgroups and prediction of patient outcomes including sepsis, acute kidney injury, mechanical ventilation, acute respiratory distress syndrome, and more. [10-17] However, to date, this methodology has only been applied in a limited fashion to the highly complex and heterogenous nature of ICU medication regimens. [1]

Critically ill patients are often prescribed greater than 20 medications, with many deemed high-risk for patient harm by the Institute of Safe Medication Practices. [18-21] Further, it has been estimated that each day, a critically ill patient will suffer at least one medication related error, with the associated adverse drug events doubling the risk of mortality. [20,21] Medication therapy optimization has significant potential to improve patient outcomes and reduce healthcare costs. [1,2] Thus, the development of novel prediction models with granular medication information to predict adverse events and direct resources is warranted. [22] However, identifying patterns associating medication therapy with patient outcomes within the vast amounts of data generated by ICU patients has remained a challenge, and to date, no AI/ML models have incorporated comprehensive ICU medication regimens into their analyses. [23]

We hypothesized that a similar approach as has been explored with other disease states of critical illness could be applied to ICU medications. Here, we sought to identify novel pharmacophenotypes using unsupervised machine learning to cluster medications used in the ICU and explore their relationship to patient-centered outcomes.

Methods

Study sample

Patients were drawn from the University of North Carolina Health System, an integrated healthcare delivery system where clinical care is managed via a comprehensive electronic health record (EHR). Patients were included if they were ≥ 18 years old with an ICU admission greater than 24 hours between October 2015 - October 2020. ICUs included medical, surgical, neurosciences, and burn. The hospitals varied including community hospitals and academic medical centers. Only the index ICU admission per each patient was considered in this analysis. The institutional review board at The University of Georgia approved this study and included waiver of consent (PROJECT00002652), and all methods were performed in accordance with the relevant guidelines and regulations.

The EHR was queried for patient demographics, medication information, and patient outcomes. Patient demographics included age, sex, admission diagnosis, ICU type, and Acute Physiology and Chronic Health Evaluation II. Medication information including drug, dose, route, duration, and timing of administration were recorded. Patient outcomes included mortality, hospital length of stay, development of

delirium (defined by CAM-ICU positive score), duration of mechanical ventilation, duration of vasopressor use, and acute kidney injury (defined by presence of renal replacement therapy or a serum creatinine greater than 1.5x baseline).

Feature Extraction

Patient demographics: There were 30,550 given medication entries in the dataset from a total of 991 patients. A total of 440 unique medications were included when generic drug names were used and when dose and route information were excluded (e.g., cefepime 1gm and 2gm were counted under the feature of cefepime). Medication records from the raw dataset included a variety of medication administration record (MAR) actions including “given”, “missed”, “hold,” etc. To ensure this analysis only included records of medication that were actually administered to the patient (not just ordered), only the entries where the medication action label corresponded to "Given", "New Bag", "Restarted", or "Rate Change" were used for the analysis. Some entries contained "free-text" for ICU personnel communication purposes and were discarded. Additionally, duplicate and incomplete entries were filtered out. After cleaning the dataset, the data were transformed into a binary (boolean) vectored form where the 440 unique medications were assigned as the rows, and 991 patients were assigned as the columns. For each patient, a binary value of 1 was assigned to indicate whether the patient received a particular drug. For patient outcomes, the labels for categorical features were relabeled as numeric values. In the cases of unknown or missing entities, these were replaced with “negative” or “no.” The entire mapping of original labels to new labels is provided in **Appendix Table 1**.

Unsupervised learning approach

Medication clustering: After performing principal component analysis (PCA) on the large, binary medication dataset, the Restricted Boltzmann Machine was utilized to further enrich the latent feature space, which we used as input to the hierarchical clustering algorithm to support the novel discovery of unique pharmacotherapy profiles. [24]

Principal Component Analysis. During PCA, each of the 440 unique medications was treated as an independent variable. PCA is a widely used dimensionality reduction technique to reduce the dimensionality of a dataset with p random variables to q, which is the desired number of variables. [25] The optimal number of principal components was selected after plotting the explained variance against the number of principal components (see **Appendix Figure 1)**. The number of principal components was selected as 150 to maintain a sufficient amount of variance (approximately 75%) in the data while significantly reducing the dimensionality.

Restricted Boltzmann Machine (RBM). Restricted Boltzmann Machine was used to learn unsupervised feature abstractions or ‘latent factors’ of the PCA reduced data. [26] RBM is a simple, two-layered neural network with one visible layer and one hidden layer. It is typically used for collaborative filtering as RBM is capable of learning internal representations of the input variables using unsupervised methods enabling complex relationships to be discovered in the process. For medication clustering purposes, RBM learned the relational nature among medication assignments based on the co-occurrence of medications for each patient. From each patient’s binary assignment of medications, RBM learned the hidden units to ultimately determine which nodes out of all nodes were activated or inactivated for each hidden unit. For clustering purposes, each medication is an independent node from the visible layer, and connections that are activated to the hidden layer indicate cluster assignment (see **Figure 1**). For example, if acetaminophen (from the visible layer) and Cluster 1 (from the hidden layer) connection was activated, acetaminophen would be assigned to Cluster 1. After assigning medications to each cluster from the created hidden layers, medications that were unassigned (never activated in the five hidden layers) were grouped as Cluster 6. **Table 1** lists the medications assigned to Clusters 1-5, and **Table 2** lists the unassigned medications in Cluster 6.

II. Patient clustering. After performing principal component analysis on the large, binary medication dataset, agglomerative clustering was utilized to cluster the medications.

Normalized medication cluster distribution. For each patient, the frequency of each medication cluster was counted (see **Figure 1**). To obtain a normalized medication cluster distribution for each patient, the frequency table was normalized by the total number of medications taken by each patient. This normalized medication cluster distribution was used as a derived feature for patient clustering.

Hierarchical agglomerate clustering. The normalized medication cluster distribution was used to cluster patients using Hierarchical Agglomerative Clustering, which builds a tree to represent data with successor nodes. [27] For implementation, **scikit-learn 1.0.2** python library was used to obtain a total of five cluster labels. The optimal number of clusters n = 5 was selected from visual inspection of the dendrogram (see **Figure 1**), which visually illustrates the hierarchical relationship between the entries (see **Figure 1**). **Table 3** describes relevant demographic and outcomes information for each cluster.

Validation of clusters

Upon selection of the optimal number of clusters, the validity of these clusters as clinically meaningful subgroups was assessed. This surrogate validation was conducted by comparing patient outcomes with medication data to see if clinically relevant characteristics were distinguishable.

Wilcoxon rank sum and signed rank tests were performed for continuous characteristics. Fisher's Exact tests were performed for categorical characteristics. Holm's adjustment of p-values was applied to the comparisons within each outcome to control the familywise error rates. Significance was assessed at p-value < 0.05. A notable finding was that two groups of clusters (Patient Clusters 1,5 and Patient Clusters 2,4) appear to have a similar length of stay while mortality rate was significantly different. Permutation multivariate analysis of variance (MANOVA) was also used to confirm if the clusters were significantly different considering all clinical outcomes simultaneously. [28]

Results

A total of 991 patients were included in the analysis. Demographic features are summarized in **Table 5.** The average was 61.2 years old (SD 17.5) with 43% female sex. The patients were managed in the medical ICU 40.7% of the time followed by 9.8% in the surgical and 9.4% in the neurosciences ICU. The mean APACHE II score at 24 hours was 14.2 (SD 6.3).

Comparison of patient and medication clusters. **Figure 1** provides a visualization of the distribution of patient clusters by medication clusters and patient outcomes, with lower mean values indicating less severe outcomes. Patient Cluster 1 had a well-rounded distribution overall when compared to other patient clusters and did not have any distinctive distribution for a particular medication cluster. In contrast, Patient Cluster 4 notably had a high distribution in Medication Cluster 6. **Figure 2** summarizes the mean medication cluster distribution for each patient cluster.

Comparison of patient clusters by clinical outcomes. Patient Cluster 3 and 5 had the least serious outcomes while Patient Cluster 2 and 4 generally had worse patient outcomes. Box plots of outcomes by patient clusters are presented in **Figure 3**. An interesting finding was that Patient Clusters 2 and 4 had no statistically significant difference in ICU length of stay, duration of mechanical ventilation, or duration of vasopressor use, but their mortality differed significantly (9.0% vs. 21.9%, $p < 0.0018$). Patient Cluster 4 had a mortality rate of 21.9% compared with the rest of the clusters ranging between 2.5-9% (see **Figure 4**). Patient Cluster 4 also had the highest number of outliers (see **Appendix Figure 2)**. The difference of ICU duration between Patient Clusters 1 and 5 and Patient Clusters 2 and 4 were statistically insignificant. Significance of the differences between patient clusters are summarized in **Table 4**. Permutation MANOVA further confirmed these differences ($p < 0.001$) (see **Appendix Table 3**).

Discussion

In the first unsupervised machine learning analysis of critically ill patients and their medication regimens, five unique patient clusters were identified with significant differences in patient acuity and outcomes. Six pharmacophenotypes were identified, and each patient cluster displayed a unique distribution of these six pharmacophenotypes. This study is the first to apply artificial intelligence to the complete medication list of ICU patients and demonstrates the ability to appropriately categorize patients with their outcomes, which lays the groundwork for future investigations.

Critically ill patients are medically complex with requisitely complex medication regimens. The significant challenges to characterizing complex, heterogeneous ICU medications in a meaningful way to drive clinical decision making parallel the challenges of managing and researching complex ICU syndromes like ARDS and sepsis. Indeed, it was reported that 62 of 76 randomized-controlled trials evaluating mortality showed no significant difference and just three of those positive studies have been accepted into practice. [29] Similar findings have been paralleled in ARDS. [30] Thoughtful editorials on this statistically unlikely preponderance of negative results have been published, and although common reasons for negative ICU studies likely account for some of these negative trials (e.g., underpowered studies, need for the use of a more conservative p-value cut-off), these statistical explanations ignore the potentially biological ones, wherein the target of an intervention is absent due to limitations in specificity of diagnosis, animal models of disease, or understanding of underlying pathophysiology. [31–33] We would like to propose another relevant driver of patient outcomes that is generally unaccounted for in both RCTs and predictive modeling studies: the complete ICU medication regimen. Traditionally, ICU medications are often thought to be direct results of critical illness (e.g., a septic patient with a high lactate is prescribed broad-spectrum antibiotics and vasopressors). However, this simplified pathway does not incorporate that ICU medications are also independent risk factors for ICU complications that

worsen patient outcomes (e.g., this septic patient develops acute kidney injury, which may be due to the shock state or the use of nephrotoxic medications or the combination). Thus, when making medication-related decisions, medications must be thought of as both treatments and causes of outcomes (see Fig. 5). Aside from overt medication errors, ICU medications are associated with significant ICU complications that increase risk of mortality and length of stay including ICU delirium, fluid overload, acute kidney injury, etc. [34–37] Ultimately, the benefits to medications used to manage critical illness must be balanced by mitigating the harms of those same treatments. Because medications in the ICU are always used in combination with other medications and interventions, identifying which medication and which medication combinations confer less risk for ICU complications has the potential to guide safer medication use. However, the dynamic relationships among patients, medications, and outcomes have been difficult to delineate given the inherent complexities and largess of ICU patient care and the data generated in that process.

Phenotyping, especially when conducted through artificial intelligence methods, has significant potential to overcome these challenges. When Calfee et al. used biomarker based phenotyping in a re-analysis of a large randomized-controlled trial evaluating simvastatin (a trial that notably had previously shown negative results), differential treatment response wherein one phenotype showed mortality benefit from simvastatin was observed. [38] Moreover, these ARDS phenotypes also showed differential treatment response to fluid management strategy. [39] Similarly, artificial intelligence methods have demonstrated the presence of unique clusters in shock, sepsis, and fluid overload. [40,41] Notably, Seymour et al. demonstrated that the results of three major randomized controlled trials were sensitive to the sepsis phenotypes they derived via unsupervised machine learning methods. Another series of shock sub-phenotypes were characterized by features associated with common ICU interventions (e.g., “well resuscitated” or “still hypovolemic”) that upon appropriate validation could yield highly relevant insights for bedside decision making. [41] Our cluster pipeline driven by unsupervised feature learning using RBM and hierarchical clustering categorized medications into five unique clusters, with the remaining medications creating a sixth category. Of the patient clusters, Clusters 2 and 4 had the highest acuity, as measured by APACHE II. This high acuity was accompanied by significantly worse outcomes, including length of stay, ICU length of stay, presence of delirium and fluid overload, and need for mechanical ventilation. Interestingly, despite being similar, Patient Cluster 4 had a mortality rate over twice as high as Cluster 2. When evaluating the distribution of pharmacophenotypes, Cluster 4 had the highest density of Medication Cluster 6 and limited representation among the other five clusters. This particular pharmacophenotype contains many of the medications classically associated with ICU care including vasopressors and broad-spectrum antibiotics. Conversely, Cluster 3 had the lowest acuity and best outcomes and also had the lowest density of all the pharmacophenotypes. Medication regimen complexity, as measured by the MRC-ICU, has been previously incorporated into machine learning prediction models along with other relevant patient characteristics and resulted in improved mortality prediction in a small cohort of patients. [42] In this study, medication regimen complexity was highest in Patient Clusters 2 and 4, which is in line with previous investigations of MRC-ICU that used traditional inferential statistics to demonstrate a relationship between increasing medication regimen complexity and increased mortality, length of stay, and fluid overload as well as increased need for critical care pharmacist interventions to optimize the medication regimens. [43–48] Taken together, the methodologies in this study appear to be able to appropriately group degree of critical illness (i.e., acuity) with degree of intervention intensity (e.g., mechanical ventilation, medications) with patient outcomes (e.g., mortality). This congruence sets the foundation for future investigations to predict ICU complications based on unique medication combinations that deleteriously affect patient outcomes.

This study has several limitations. First, dose and route information for medications was not included and establishing uniform means of describing and comparing ICU medication dosing strategies and validating in external datasets remains an area of future work. We did not utilize more robust applications of RBMs, such as incorporating Gaussian-Bernoulli RBM. [24] We assumed homogeneity across medication regimens; however, in practice this may be a highly complex and noisy interaction: therefore, in future work, we seek to utilize Trust Discover platforms to generalize pharmacotherapy profiles that are normalized independent of clinician and institutional bias. [49] Finally, causal inference cannot be assessed by the current study, so it is unknown whether the high mortality observed in Patient Cluster 4 was partly caused by the unique distribution of pharmacophenotypes versus other factors (although notably, Cluster 4 shared similarities among groups). Even with these limitations, this analysis marks the first time the complete medication profile has been incorporated into outcomes analysis for ICU patients.

Conclusion

The medication regimens of critically ill patients have unique pharmacophenotypes. Given the significant role of medication therapy in patient outcomes, delineating the complex relationships among patients, medications, and outcomes using artificial intelligence warrants future investigation.

Declarations

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Tables

Table 1

Medication Clusters Assigned by Restricted Boltzman Machine

Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Amitriptyline	Alteplase	Adenosine	Aluminum-mag hydroxide-simethicone	Acyclovir
Atorvastatin	Atovaquone	Amiodarone	Amitriptyline	Benzoin-aloe vera-storax-tolu balsam
Biotin	Barium sulfate	Ampicillin	Amphotericin B Liposomal Amphotericin B	Bupivacaine
Buprenorphine	Basiliximab infusion	Anakinra	Aspirin	Chlorothiazide
Cefazolin	Bumetanide	Biotin	Azelastine	Diatrizoate meglumine-Diatrizoate sodium
Cefuroxime	Cefuroxime	Bivalirudin	Bupivacaine	Dutasteride
Chlorothiazide	Citalopram	Cefazolin	Buspirone	Ertapenem
Cholecalciferol	Cyclosporine	Cefdinir	Calcium carbonate	Fluticasone
Clindamycin	Dextrose	Cetirizine	Carbidopa	Gentamicin
Emtricitabine-Tenofovir	Docusate sodium	Clobazam	Citrate dextrose	Glucose
Ergocalciferol	Dutasteride	Dopamine	Codeine	Hydrocodone
Melatonin	Fentanyl	Droxidopa	Conjugated-estrogens	Linezolid
Metolazone	Ferrous sulfate	Esomeprazole Magnesium	Daunorubicin	Magnesium oxide
Osimertinib	Gentamicin	Estradiol	Hydroxychloroquine	Metformin
Oxybutynin	Glucose	Ganciclovir	Lactobacillus	Methylprednisolone
Pantoprazole	Hydrocortisone	Indomethacin	Mafenide	Nicotine
Potassium/Sodium phosphates	Hydroxychloroquine	Mirtazapine	Metformin	Prasugrel
Sennosides	Hydroxyurea	Moxifloxacin	Montelukast	Racemic epinephrine
Silver sulfadiazine	Lopinavir-ritonavir	Multivitamin	Neomycin	Sotalol
Thrombin	Methocarbamol	Nicardipine	Nicardipine	Sucralfate
	Midodrine	Olanzapine	Nifedipine	Theophylline
	Oxcarbazepine	Oxycodone-acetaminophen	Peramivir	Valacyclovir
	Pentamidine	Racepinephrine	Polyethylene glycol	
	Simvastatin	Rivaroxaban	Potassium citrate	
	Ticagrelor	Sodium acetate	Pravastatin	
	Ursodiol	Sodium chloride	Sodium chloride	
		Sumatriptan	Sodium phosphates	
		Tamsulosin	Tamsulosin	
		Trazodone		
		Triamcinolone		
		Venlafaxine		

Table 2

Cluster 6 - Medications unassigned through Restricted Boltzman Machine

Acetaminophen	Calcium gluconate	Dornase alfa
Acetazolamide	Carboplatin	Dorzolamide
Acetylcysteine	Carvedilol	Doxazosin
Albumin	Cefepime	Doxycycline
Albuterol sulfate	Ceftaroline	Dronabinol
Allopurinol	Ceftazidime	Duloxetine
Alprazolam	Ceftriaxone	Econazole
Alvimopan	Celecoxib	Enalapril maleate
Amantadine	Cellulose	Enalaprilat
Aminocaproic acid	Cephalexin	Enoxaparin
Amlodipine	Chlordiazepoxide	Epinephrine
Ammonium lactate	Chlorpromazine	Epoetin alfa
Amoxicillin	Chlorthalidone	Eptifibatide
Apixaban	Cholestyramine-aspartame	Escitalopram
Arformoterol	Cilostazol	Esmolol
Argatroban	Cinacalcet	Ethacrynate sodium
Aripiprazole	Ciprofloxacin	Ethacrynic acid
Artificial tears	Cisatracurium	Etomidate
Ascorbic acid	Cladribine	Eye preparations
Atenolol	Clevidipine	Ezetimibe
Atropine	Clobetasol	Factor VIIa
Azathioprine	Clonazepam	Famotidine
Azithromycin	Clonidine	Fat emulsion
Aztreonam	Clopidogrel	Fenofibrate
Bacitracin	Colchicine	Finasteride
Baclofen	Collagenase clostridium histolyticum	Flecainide
Balanced salt irrigation solution	Cyanocobalamin	Fluconazole
Banana bag	Cyclobenzaprine	Fludrocortisone
Belladonna alkaloids-opium	Cyclosporine	Fluorometholone
Bendamustine	Cytarabine	Fluoxetine
Benzocaine	Dantrolene	Folic acid
Benzonatate	Daptomycin	Fondaparinux
Benztropine	Desmopressin	Formoterol fumarate
Bicalutamide	Dexamethasone	Fosaprepitant
Bisacodyl	Dexmedetomidine	Fosfomycin tromethamine
Brentuximab vedotin	Dextromethorphan-guaifenesin	Fosphenytoin
Brimonidine	Diazepam	Furosemide
Bromocriptine	Dibucaine	Gabapentin
Budesonide	Diclofenac	Gadobenate dimeglumine

Bupropion	Digoxin	Gadoterate meglumine
Butalbital-acetaminophen-caffeine	Diltiazem	Glimepiride
Butamben-tetracaine-benzocaine	Diphenhydramine	Glipizide
Calcitonin	Diphenoxylate-atropine	Glucagon
Calcitriol	Dipyridamole	Glycerin
Calcium acetate	Divalproex	Glycopyrrolate
Calcium chloride	Dobutamine	Guaifenesin
Calcium citrate-vitamin d3	Donepezil	Guar gum oral packet
		Haloperidol
Heparin	Meropenem	Methylphenidate
Hydralazine	Potassium phosphate	Metoclopramide
Hydrochlorothiazide	Pramipexole	Metronidazole
Hydromorphone	Prednisolone acetate	Micafungin
Hydroxyzine	Prednisolone sodium phosphate	Midazolam
Ibuprofen	Prednisone	Milrinone
Immune globulin (IgG)	Pregabalin	Minocycline
Insulin	Prenatal vitamin with calcium no.72-iron	Mometasone-formoterol
Iodixanol	Prochlorperazine	Morphine
Iohexol	Promethazine	Mupirocin
Iopamidol	Propofol	Mycophenolate
Ipratropium	Propranolol	Naloxone
Iron sucrose	Protamine	Naproxen
Isoproterenol infusion	Prothrombin complex (kcentra) intermittent infusion	Nimodipine
Isosorbide dinitrate	Pyridostigmine bromide	Nintedanib
Isosorbide mononitrate er	Pyridoxine	Nitroglycerin
Ketamine	Quetiapine	Nitroprusside
Ketorolac	Raltegravir	Norepinephrine
Labetalol	Ranolazine	Nortriptyline
Lacosamide	Rasburicase	Nxstage fluids
Lactase	Remdesivir	Nystatin
Lactated ringers	Rifampin	Octreotide
Lactulose	Rifaximin	Omeprazole
Lamotrigine	Risperidone	Ondansetron
Lanthanum	Rizatriptan	Oseltamivir
Latanoprost	Rocuronium	Oxacillin
Levalbuterol	Ropinirole	Oxandrolone
Levetiracetam	Rosuvastatin	Oxycodone
Levofloxacin	Saliva stimulant agents	Oxymetazoline
Levothyroxine	Sertraline	Paclitaxel

Lidocaine	Sevelamer	Papaverine
Lipase-protease-amylase	Silver nitrate	Paroxetine
Liraglutide	Simethicone	Pentobarbital
Lisinopril	Smog enema	Perflutre
Lithium carbonate	Sodium bicarbonate	Phenazopyridine
Loperamide	Sodium ferric gluconate	Phenobarbital sodium
Loratadine	Sodium hypochlorite	Phenol
Lorazepam	Sodium polystyrene sulfonate	Phenylephrine
Losartan	Spironolactone	Phenytoin sodium extended
Lovastatin	Succinylcholine chloride	Phytonadione
Magnesium citrate oral solution	Sucralfate	Piperacillin-tazobactam
Magnesium hydroxide	Sugammadex	Posaconazole
Magnesium sulfate	Sulfamethoxazole	Potassium & sodium phosphates
Mannitol	Tacrolimus	Potassium chloride
Matrix hemostatic sealant	Methadone	Tamoxifen
Medroxyprogesterone	Methimazole	Tbo-filgrastim
Meloxicam	Methotrexate sodium	Teduglutide
Memantine	Methylene blue	Terazosin
Menthol		Tetanus-diphtheria toxoids-td
Meperidine		Tezacaftor
Methylnaltrexone		Thiamine

Thyroid (pork)

Tiotropium bromide

Tobramycin

Tocilizumab

Topiramate

Torsemide

Tramadol

Triamterene

Valganciclovir

Valproic acid

Valsartan

Vancomycin

Vasopressin

Vecuronium

Verapamil

Vitamin a

Vitamin b

Voriconazole

Warfarin
Zinc sulfate
Ziprasidone
Zolpidem

Table 3

Demographic Characteristics by Patient Cluster

Cluster	1 (N = 234)	2 (N = 201)	3 (N = 115)	4 (N = 247)	5 (N = 194)
Age (years)	61.5 ± 17.5	61.1 ± 16.8	67.8 ± 14.9	57.0 ± 18.1	62.4 ± 17.8
Sex (female)	109 (46.5)	84 (41.7)	35 (30.4)	119 (48.1)	81 (41.7)
ICU Type					
Medical	73 (31.2)	74 (36.8)	32 (27.8)	133 (53.8)	92 (47.4)
Surgical	16 (6.8)	23 (11.4)	3 (2.6)	35 (14.1)	20 (10.3)
Neurosciences	25 (10.6)	17 (8.4)	16 (13.9)	14 (5.6)	21 (10.8)
Burn	34 (14.5)	12 (5.9)	7 (6.0)	11 (4.4)	6 (3.0)
Other	2 (0.8)	8 (3.9)	2 (1.7)	7 (2.8)	3 (1.5)
Admission Diagnosis					
Sepsis/Infection	8 (3.4)	23 (11.0)	4 (3.4)	42 (17.0)	20 (10.3)
Pulmonary	29 (12.3)	19 (9.4)	5 (4.3)	49 (19.8)	22 (11.4)
Neoplasm	18 (7.6)	9 (4.4)	5 (4.3)	16 (6.4)	14 (7.2)
Gastrointestinal	15 (6.4)	22 (10.9)	8 (6.9)	27 (10.9)	11 (5.7)
Cardiovascular	67 (28.6)	55 (27.3)	43 (37.3)	30 (12.1)	49 (25.3)
Other	14 (5.9)	17 (8.4)	6 (5.2)	14 (5.6)	8 (4.1)
Renal	13 (5.5)	13 (6.4)	5 (4.3)	9 (3.6)	7 (3.6)
Neurology	24 (10.2)	23 (11.4)	27 (23.4)	36 (14.5)	29 (15.0)
Endocrine	8 (3.4)	0 (0.0)	2 (1.7)	5 (2.0)	9 (4.6)
Trauma	38 (16.2)	20 (9.9)	10 (8.7)	19 (7.6)	24 (12.4)
APACHE II at 24 hours	13.0 ± 6.4	15.4 ± 6.3	11.3 ± 4.6	16.3 ± 6.6	13.7 ± 5.7
MRC-ICU at 24 hours	9.7 ± 7.7	12.3 ± 8.5	5.5 ± 3.8	12.5 ± 7.7	8.7 ± 6.4
Mortality	6 (2.56)	18 (8.96)	3 (2.61)	54 (21.86)	16 (8.25)
Hospital length of stay (days)	8.8 ± 11.9	14.6 ± 20.2	4.8 ± 3.4	15.9 ± 31.1	9.6 ± 9.0
ICU length of stay (days)	4.2 ± 8.9	6.2 ± 8.6	2.4 ± 1.5	7.3 ± 14.3	3.7 ± 3.4
Presence of delirium n (%, total)	41 (18.6, 220)	75 (39.6, 189)	10 (9.4, 106)	115 (53.4, 215)	52 (29.3, 177)
Acute kidney injury n (%, total)	21 (9.1, 232)	39 (19.4)	3 (2.6)	73 (30)	18 (9.3)
Duration of vasopressors support (days)	1.3 ± 0.8	1.8 ± 1.5	1.0 ± 0.0	1.8 ± 1.7	1.3 ± 0.5
Presence of mechanical ventilation	54 (23.0)	89 (44.2)	3 (2.6)	122 (49.3)	44 (22.6)
Duration of mechanical ventilation (days)	1.6 ± 3.1	5.3 ± 9.6	2.7 ± 3.3	8.4 ± 18.1	3.5 ± 4.3
Presence of fluid overload (%, total)	9 (4.5, 199)	26 (13.8, 188)	4 (4.2, 94)	52 (23.9, 217)	14 (8.6, 162)
Data are presented as n (%) or mean ± standard deviation (SD) unless otherwise stated.					

Table 4

Pair-wise comparison of differences in patient outcomes by patient cluster

		Continuous Outcomes					Categorical Outcomes			
1st Cluster	2nd Cluster	Length of stay (days)	Duration of mechanical ventilation (days)	Duration of vasopressor support (days)	APACHE II score (first 24h)	MRC-ICU	Death	Acute kidney injury	Delirium	Mechanical Ventilation
1	2	<0.0001	<0.0001	0.0002	0.0003	0.0012	0.0312	0.0130	<0.0001	<0.0001
1	3	<0.0001	<0.0001	0.0370	0.1695	<0.0001	1.0000	0.0760	0.0692	<0.0001
1	4	0.0009	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
1	5	0.4803	0.6110	0.8065	0.1904	1.0000	0.0689	1.0000	0.0380	0.6700
2	3	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.1353	<0.0001	<0.0001	<0.0001
2	4	0.4803	0.0570	0.3478	0.1904	1.0000	0.0018	0.0630	0.0278	0.6700
2	5	0.0007	<0.0001	0.0002	0.0328	0.0002	1.0000	0.0210	0.0692	<0.0001
3	4	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
3	5	<0.0001	<0.0001	0.0583	0.0015	<0.0001	0.1536	0.0760	0.0003	<0.0001
4	5	0.0245	<0.0001	<0.0001	0.0002	<0.0001	0.0009	<0.0001	<0.0001	<0.0001

Wilcoxon rank sum and signed rank tests were performed for continuous variables. Fisher's Exact tests were performed for categorical outcomes. Holm's adjustment of p-values was applied to the comparisons within each outcome to control the familywise error rates.

Table 5

Summary of patient population

Feature	N = 991
Age	61.2 (17.5)
Female	428 (43.2)
ICU Type	
Medical	404 (40.7)
Surgical	97 (9.8)
Neurosciences	93 (9.4)
Burn	70 (7.1)
Other	22 (2.2)
Admission Diagnosis	
Sepsis/Infection	97 (9.8)
Pulmonary	124 (12.5)
Neoplasm	62 (6.3)
Gastrointestinal	83 (8.4)
Cardiovascular	244 (24.6)
Dermatology	59 (6.0)
Renal	47 (4.7)
Neurology	139 (14.0)
Endocrine	24 (2.4)
Trauma	111 (11.2)
APACHE II at 24 hours	14.2 (6.3)
MRC-ICU at 24 hours	10.2 (7.6)
Mortality	97 (9.8)
Hospital length of stay (days)	11.4 (19.7)
ICU length of stay (days)	5.1 (9.5)
Presence of delirium during ICU stay (days)	293 (29.6)
Presence of AKI during ICU stay	151 (25.2)
Duration of vasopressors support (days)	0.5 (1.0)
Presence of mechanical ventilation	318 (32.1)
Duration of mechanical ventilation (days)	5.6 (12.8)
Presence of fluid overload	105 (12.2)
Data are presented as n (%) or mean ± standard deviation (SD) unless otherwise stated.	

Figures

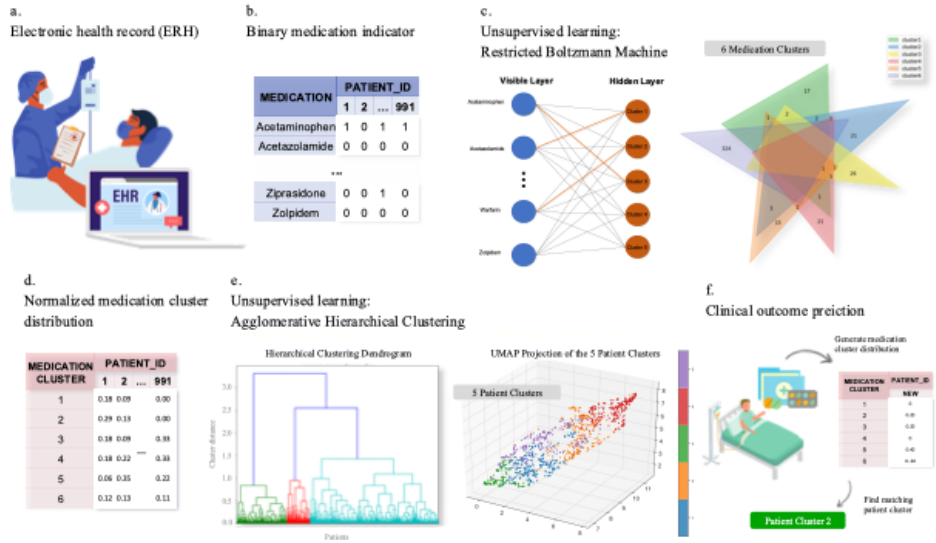

Figure 1

Pharmacophenotype derivation workflow.

a) When medications are ordered by the clinician for ICU patients, all administered medications are recorded and stored in the electronic health record (EHR) system. b) The medication data from the EHR was preprocessed to create a binary indicator matrix that contains all unique medications taken by a total of 991 patients. c) Five medication clusters were created using unsupervised learning model (Restricted Boltzmann Machine). The layers that are not turned "on" (indicated in orange) to any hidden layers are grouped as an extra sixth cluster. d) For each patient, the frequency of each medication cluster was counted and normalized by the total medications taken by each patient during their stay. e) The normalized medication cluster distribution of each patient is used as a feature to agglomerative hierarchical clustering to develop novel pharmacophenotypes of critically ill patients. f) These novel pharmacophenotypes can be used to predict clinical outcomes of new patients based on their medication regimens.

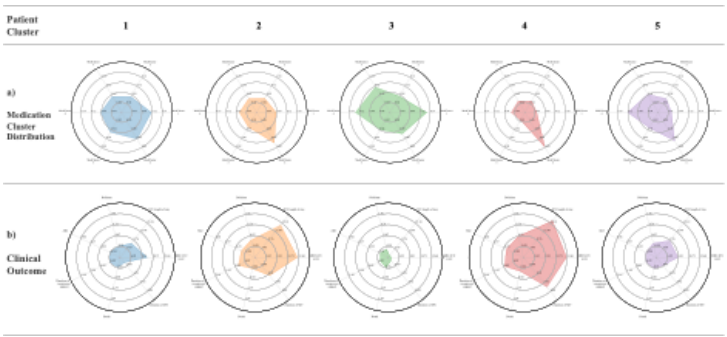

Figure 2

Radial plot distributions in each patient cluster.

a) *Radial plot of the mean medication cluster distribution in each patient cluster.* Patient Cluster 1 has a well-rounded distribution overall when compared to other patient clusters without any outstanding distribution of a particular medication cluster comparably. In contrast, Patient Cluster 4 notably has a high distribution in Medication Cluster 6. b) *Radial plot of the mean clinical outcomes in each patient cluster.* The lower the mean value, the less severe the outcome was for each clinical outcome category. Thus, Patient Cluster 3 and 5 can be interpreted to have the least serious outcomes while Patient Cluster 2 and 4 generally had worse outcomes.

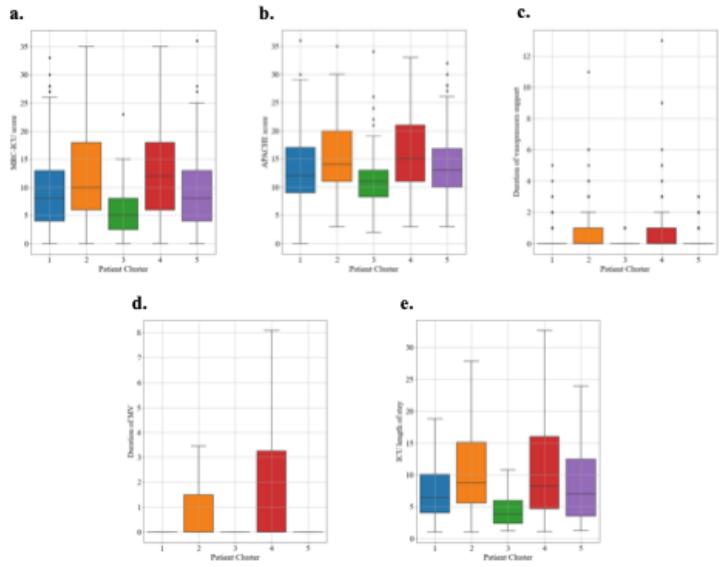

Figure 3

Boxplots of MRC-ICU, APACHE II, and patient outcomes by patient cluster.

a) MRC-ICU score evaluated at 24 hour. b) APACHE score evaluated at 24 hour. c) Total days of vasopressor support patient received during admission. d) Total days patient was on mechanical ventilation. e) total days in the ICU. For panel d and e, outliers have been removed to improve visibility of the distribution (full box plots are available in the Appendix Figure 2).

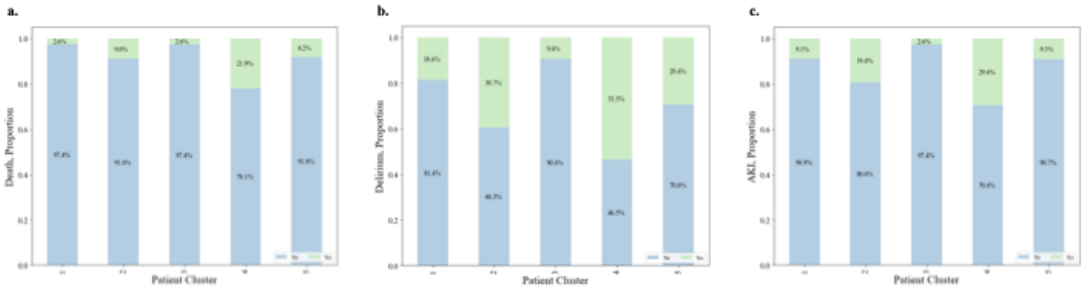

Figure 4

Stacked bar plots showing proportion of patient outcome (categorical) by patient cluster. Any patients with unknown or unreported outcome were removed for analysis.

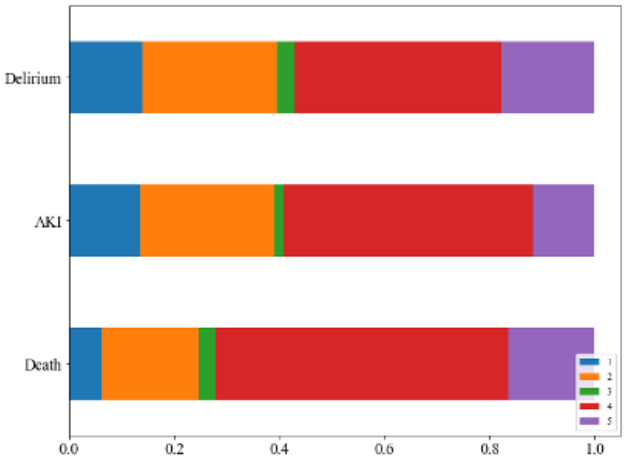

Figure 5

Legend not included with this version

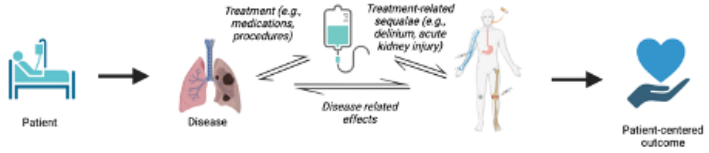

Figure 6

Patient – Treatment – Outcome Pathway

The unique interactions of medication interventions with patient disease must be accounted for when predicting or studying patient-centered outcomes.