Towards timely Alzheimer's diagnosis: a clinical data-driven approach to biomarker discovery

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INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder characterized by a progressive decline in cognitive function and memory [1]. The prevalence of dementia, mostly attributed to AD, is increasing in the United States and globally.

Early symptoms are often non-specific and go unnoticed. Traditional diagnosis relies on clinical and cognitive assessments, which are both subjective and often imprecise [2].

Currently, no objective and reliable biomarkers exist for the detection of AD in its early stages. Our study fills this gap in the field and proposes lab-based biomarkers that may be used to diagnose AD by analyzing retrospectively collected critical care medical data from the MIMIC-IV database [3].

The detection of AD in its early stages will allow for early clinical intervention and the possibility of more effective and robust management of this complex disorder prior to its progression.

METHODS

We utilized the MIMIC-IV database that includes critical care data from 40,000 racially and ethnically diverse patients admitted to intensive care units at the Beth Israel Deaconess Medical Center. For each lab (n=1600+), MIMIC-IV was filtered for patients with a primary diagnosis of AD and age- and sex-matched non-psychiatrically ill control (CTL) patients.

Each case was matched to four CTLs. The means and standard deviations for each lab of interest was calculated. Welch's two sample t-test was used to compare means and standard deviations in AD vs. CTL groups. Effect sizes (ES) were also calculated to further assess the practical significance of our results.

RESULTS

	AD vs. CTL	Females AD vs. CTL	Males AD vs. CTL
Total Labs	477	227	210
Significant Labs (p<0.05)	51	22	22
Labs with Moderate-Large ES	22	6	9
Moderate-Large ES Range	0.27-1.16	0.35-0.48	0.26-0.49

AD vs. CTL	
Lab | Fluid | Units	**ES**
Acetaminophen | Blood | ug/mL	0.84
Albumin | Urine | mg/dL	0.47
Albumin/Creatinine | Urine | mg/g	0.61
CA-125 | Blood | U/mL	0.51
Calculated TBG | Blood | Ratio	1.16
Chloride | Blood | mEq/L	0.32
Chloride | Urine | mEq/L	0.29
Cholesterol, LDL, Calculated | Blood | mg/dL	0.27
Cholesterol, Total | Blood | mg/dL	0.34
Fibrinogen, Functional | Blood | mg/dL	0.47
Glucose | Urine | mg/dL	0.32
Haptoglobin | Blood | mg/dL	0.47
Osmolality | Urine | mOsm/kg	0.44
Other Cells | Blood | %	0.33
Parathyroid Hormone | Blood | pg/mL	0.32
Phenytoin, Percent Free | Blood | %	1.01
Sedimentation Rate | Blood | mm/hr	0.45
Sodium | Blood | mEq/L	0.35
Sodium | Urine | mEq/L	0.33
Uptake Ratio | Blood | Ratio	1.14
Urea Nitrogen | Urine | mg/dL	0.35
Valproic Acid | Blood | ug/mL	0.60

ES Ranges Utilized in the Study	
0.0-0.25	Small ES
0.26-0.75	Moderate ES
>0.76	Large ES

Females AD vs. CTL	
Lab | Fluid | Units	**ES**
Chloride | Blood | mEq/L	0.37
Fibrinogen, Functional | Blood | mg/dL	0.48
Haptoglobin | Blood | mg/dL	0.46
Osmolality | Urine | mOsm/kg	0.46
Sodium | Blood | mEq/L	0.35
Sodium | Urine | mEq/L	0.35

Males AD vs. CTL	
Lab | Fluid | Units	**ES**
Fibrinogen, Functional | Blood | mg/dL	0.46
Haptoglobin | Blood | mg/dL	0.49
Hematocrit | Blood | %	0.26
Hemoglobin | Blood | g/dL	0.27
Osmolality | Urine | mOsm/kg	0.41
Red Blood Cells | Blood | m/uL	0.26
Sodium | Blood | mEq/L	0.35
Sodium | Urine | mEq/L	0.30
Urea Nitrogen | Blood | mg/dL	0.28

DISCUSSION

- Potential lab-based biomarkers for AD were fell in three major diagnostic categories: kidney function (urea nitrogen), cardiovascular (cholesterol), and electrolyte/metabolic balance (chloride, glucose)
- Among the three comparison groups, the AD vs. CTL group had the most significant labs with moderate to large ESs (n=22) as well as the broadest ES range (0.27-1.16).
- Five labs were common across all comparison groups: functional fibrinogen (blood), haptoglobin (blood), urine osmolality, blood sodium, and urine sodium.
- An assessment of significant labs between females and males showed overlap; however, males were distinguished by the broader diagnostic category of hematology, indicating the importance of considering sex in biomarker analysis for AD.

REFERENCES

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